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ÉTUDE TOPOGRAPHIQUE DES RÉACTIONS ÉLECTROENCÉPHALOGRAPHIQUES CONDITIONNÉES CHEZ L'HOMME

(Essai d'Interprétation Neurophysiologique)

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La conception pavlovienne de la dynamique corticale est basée sur la distinction des deux processus fondamentaux d'excitation et d'inhibition dont les rapports réciproques en fonction du temps et de l'espace ont pu être étudiés grâce au réflexe conditionnel.

Cette méthode, cependant, ne fournit qu'une expression indirecte, périphérique, de l'excitation et de l'inhibition centrales qui se présentent à l'observateur sous la forme d'une activité réflexo-conditionnée accrue ou diminuée. On s'explique donc que les expérimentateurs se soient très tôt orientés vers l'étude directe, électroencéphalographique, de ces phénomènes chez l'homme (Durup et Fessard 1935; Loomis, Harvey et Hobart 1936). Un grand nombre de travaux [1] ont été consacrés depuis lors à cette étude jusqu'au Colloque qui s'est tenu à Marseille en novembre 1955 pour faire le point actuel de la question.

Il est apparu au cours de ce Colloque que les recherches effectuées chez l'homme jusqu'à ce jour étaient insuffisantes dans la mesure où elles ne s'adressaient qu'au seul rythme alpha qui occupe les régions occipito-pariéto-temporales des deux hémisphères et qui réagit *globalement* et de façon *bilatérale* à la stimulation visuelle. Une telle façon de procéder exclut en effet toute possibilité d'étude topographique et chronologique des phénomènes bio-électriques conditionnés sur le cortex, alors que la théorie pavlovienne laisse supposer qu'ils doivent s'y distribuer de façon différente dans l'espace et dans le temps; elle implique au surplus l'utilisation d'une seule

[1] Malgré le travail si précoce de Durup et Fessard, ces études furent négligées en France, tandis qu'elles étaient poursuivies en Amérique de 1937 à 1943 (Jasper et Cruikshank 1937; Travis et Egan 1938; Knott et Henry 1941; Jasper et Shagass mai 1941 et juin 1941; Shagass 1941; Shagass et Johnson 1943). Reprises à cette époque en U.R.S.S. et au Japon, elles s'y continuent régulièrement depuis et ont donné lieu à une abondante littérature (Spielberg 1937; Beritachvili et Vorobiev 1943; Motokawa 1949; Motokawa et Huzimori 1949; Kojevnikov et Marousseva 1949; Iwama 1950; Maiortchik et Spirine 1951; Iwama et Abe 1952; Tchougounov 1952; Abe 1954; A. et C. Jus 1954-1955; Roussinov 1955; Bekhtereva 1955; B. Pavlov 1955).

variété de stimulation inconditionnelle (la lumière, qui bloque le rythme alpha) alors que, d'après l'école réflexologique, les stimuli absolus les plus simples sont au moins aussi nombreux que les systèmes sensoriels susceptibles de les analyser.

Il est encore apparu au cours du Colloque de Marseille, que les techniques employées jusqu'à ce jour étaient élémentaires et que l'étude électroencéphalographique du conditionnement ne pourrait progresser sans l'utilisation d'un grand nombre de dérivations permettant l'exploration simultanée de plusieurs régions corticales et de différentes activités somatiques (électromyogramme, électrodermogramme, électrocardiogramme et pneumogramme). Selon Grey Walter, l'analyse automatique de fréquences semble même indispensable.

C'est pour corriger ces insuffisances que nous avons décidé de reprendre entièrement le problème du conditionnement électrocortical chez l'homme en tenant compte des critiques précédentes. Ce projet ayant été élaboré au cours d'un Colloque international, il a été possible d'y faire participer des laboratoires de nationalités différentes et c'est ainsi que la réalisation du travail s'est effectuée simultanément à Leiden (Holland),[1] à Lodz (Pologne),[2] à Marseille[3] et à Minneapolis (EE. UU.),[4] avec la méthode suivante.

I — MATÉRIEL ET MÉTHODE

Au lieu de nous limiter à l'étude du blocage conditionné du rythme alpha, nous avons également envisagé celui des rythmes rolandiques et en particulier celui du rythme « en arceau » récemment individualisé par H. Gastaut (1952). Ce rythme de topographie rolandique[5] présente, en effet, la particularité essentielle de se bloquer « unilatéralement » lorsqu'on soumet l'individu à des stimulations extero et proprioceptives controlatérales. La spécificité même de ce blocage du rythme en arceau laisse donc supposer qu'il doit être possible de le conditionner au même titre que la réaction d'arrêt du rythme alpha ; au surplus le blocage conditionné du rythme en arceau pourrait fournir des données topographiques plus différenciées.

Nous avons donc sélectionné 28 sujets dont l'EEG présentait d'une part un rythme alpha continu, bloquant à l'ouverture des yeux, d'autre part un rythme en arceau rolandique continu, se bloquant à la stimulation extéroceptive de la main ou à la contraction du poing. Nous avons d'autre part retenu 32 sujets qui ne présentaient que l'un ou l'autre de ces deux rythmes (le rythme alpha le plus souvent) et qui furent utilisés pour des expériences de contrôle. Sur ces 60 individus ont été réalisées plusieurs centaines d'expériences de conditionnement.

a) Dans toutes ces expériences, le *stimulus indifférent* était représenté par un son continu de tonalité et d'intensité invariables au cours d'une même expérience chez un même sujet. L'intensité de ce son était toujours faible. Sept fois il s'agissait d'un son pur de fréquence 200 c/sec. délivré par un générateur spécial (Soneclat Alvar), une fois il s'agissait d'un son de sifflet et 10 fois d'un son complexe fourni par une sonnerie étouffée. Dans tous les cas, le stimulus indifférent était délivré avant le stimulus absolu mais continuait pendant la durée de l'application de celui-ci (chevauchement du stimulus indifférent et absolu avec précession du premier). La durée de la précession a varié, suivant les cas, de 2 à 5 sec., en restant à peu près constante pendant une même expérience.

b) Les stimuli *absolus* étaient, suivant les expériences, visuels ou somesthésiques :

i) Les stimuli *visuels* étaient représentés : soit par une lumière continue fournie par une lampe à incandescence de 150 bougies située à 1m50 du sujet dans un diffuseur, et appliquée pendant 3 sec. ; soit par une lumière intermittente fournie par un stroboscope « Épiphote » et appliquée pendant 5 sec. avec une fréquence fixe comprise entre 10 et 15 c/sec.

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1 W. Storm van Leeuwen, D. Bekkering, A. Kamp et J. Werre.

2 A. et C. Jus.

3 H. Gastaut, S. Dongier, R. Naquet, H. Regis et A. Roger.

4 F. Morrell.

5 Nous n'avons tenu compte dans la réactivité des régions rolandiques que de celle du rythme en arceau qui, ample et lent, est facile à enregistrer et à étudier ; il n'en demeure pas moins que le rythme bêta de la région rolandique réagit de la même manière (Jasper et Penfield 1949) et qu'il se « conditionne » aussi bien que le rythme en arceau auquel il est souvent associé.

ii) Les stimuli *somesthésiques* étaient représentés par le déplacement d'une main obtenu passivement en actionnant à distance une planchette ou activement en donnant l'ordre : « Serrez le poing ».[1]

c) Suivant l'effet *conditionnel* que nous désirions obtenir, les stimuli étaient combinés de la façon suivante :

« son + lumière continue ou intermittente » chez les sujets dont nous voulions conditionner le rythme alpha ;

« son + déplacement passif ou actif de la main » chez ceux dont nous voulions conditionner le rythme rolandique ;

Chez ceux, enfin, dont nous voulions conditionner les deux rythmes à la fois, nous avons employé la combinaison « son + lumière + contraction de la main pendant l'application de la lumière, suivant une instruction préalablement fournie ».[2]

Dans les expériences effectuées dans le Laboratoire de Marseille, l'accouplement de deux appareils d'EEG à 7 et 15 plumes (dont les enregistrements étaient synchronisés) a permis d'explorer simultanément les 19 électrodes actives de la disposition proposée par la Fédération Internationale des Sociétés d'EEG. Dans ces conditions techniques particulières, l'enregistrement électroencéphalographique a été fait suivant des dérivations orthogonales donnant la possibilité d'apprécier l'orientation des générateurs corticaux et a été combiné à l'inscription de l'électromyogramme, de l'électrocardiogramme, de l'électrodermogramme et du pneumogramme.

Les expériences les plus importantes effectuées à Marseille furent enfin enregistrées simultanément sur un électroencéphalographe et sur une bande magnétique afin de permettre au laboratoire de Leiden (Storm van Leeuwen) d'effectuer une analyse de fréquence automatique, simultanée, de 8 des dérivations corticales utilisées.[3]

II — PRÉSENTATION GÉNÉRALE DES RÉSULTATS ET SÉLECTION DE QUELQUES CAS

Nous n'avons admis comme manifestations électroencéphalographiques conditionnées que celles provoquées plusieurs fois de suite par le stimulus conditionnel (de 4 fois à plus de 40 fois suivant le cas). Nous avons par contre éliminé toutes les modifications de l'EEG survenant de façon sporadique, même si quelques unes d'entre elles semblaient en relation certaine avec le stimulus conditionnel. Avec des critères de sélection aussi sévères, nous n'avons trouvé que 60 pour cent de conditionnement électrocortical certain sur l'ensemble de toutes nos expériences. Il est évidemment impossible de rapporter et d'illustrer tous les protocoles des expériences que nous avons retenues et nous nous contenterons d'en présenter quelques uns avant de passer à l'étude analytique des phénomènes observés dans l'ensemble des cas.

Protocole I — Enfant G. . . ., 9 ans, troubles caractériels discrets. On demande à l'enfant de serrer le poing droit chaque fois qu'il verra une lumière s'éclairer devant ses yeux fermés. La suite des événements électroencéphalographiques est représentée sur les figures suivantes qui montrent également l'électromyogramme des muscles fléchisseurs de l'avant-bras droit et les signaux utilisés pour le conditionnement: T = ton, L = lumière, F = fin simultanée des deux stimulations. (Fig. 1a à 1i)

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[1] La combinaison « son + ordre verbal de serrer le poing » est celle utilisée par Ivanov-Smolenski pour l'étude du conditionnement moteur périphérique. Elle présente la particularité de mettre en jeu le second système de signalisation de Pavlov, c'est-à-dire le langage, et de faire dépendre le *signal absolu*, c'est-à-dire une volée d'afférences proprioceptives corticipètes, d'un réflexe conditionnellement acquis pendant l'ontogenèse (on a appris à serrer le poing dès qu'on en reçoit l'ordre).

[2] La combinaison « son + lumière + contraction de la main suivant une instruction préalable », encore plus complexe, fait ici jouer un rôle au langage intérieur et à une mémoire à long terme tenant sous sa dépendance l'exécution d'un acte volontaire différé: « je serrerai le poing quand je verrai la lumière ».

[3] Pour la technique de cette analyse spéciale, consulter le travail de Bekkering, Kamp, de Lange, Storm Van Leeuwen et Werre, publié dans les Comptes Rendus du Colloque de Marseille, 1955.

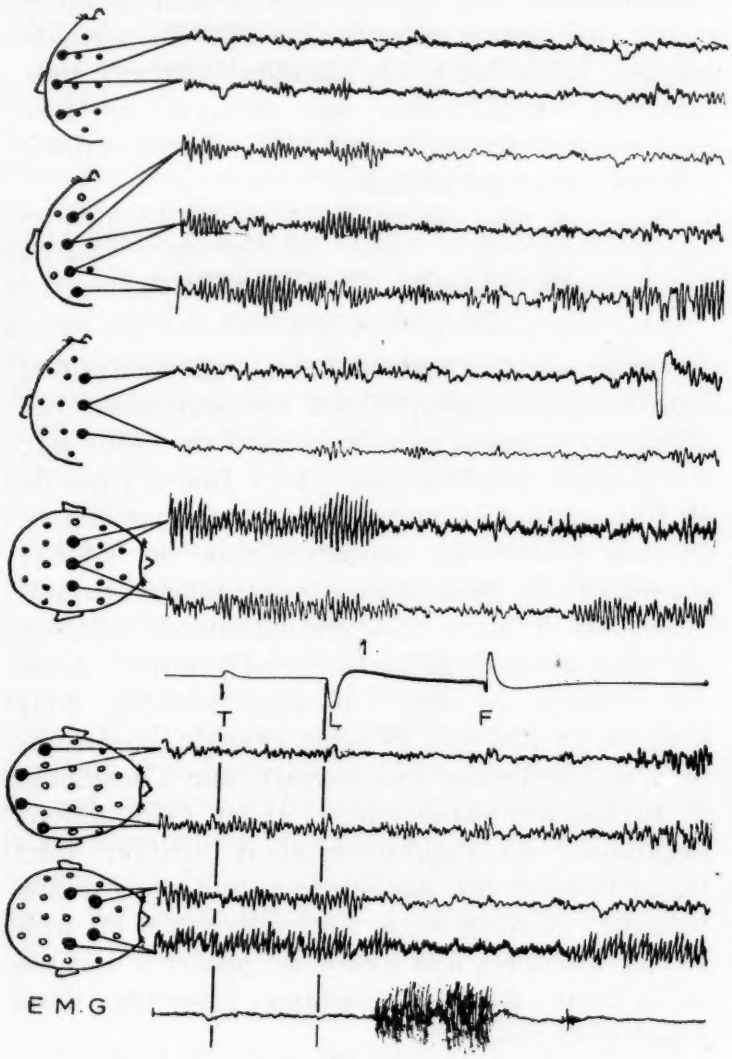


Fig. 1a

La première combinaison « son-lumière » n'entraîne aucune réaction conditionnée (le son est bien « indifférent ») mais provoque de nombreuses manifestations inconditionnées tenant au stimulus lumineux et à la contraction du poing qui l'accompagne:

a) le rythme alpha présente la réaction d'arrêt à la lumière sur les deux hémisphères en même temps.

b) le rythme rolandique, indifférent à la lumière, réagit à la contraction du poing. Sur l'hémisphère gauche il se bloque avant la contraction, traduisant la mise en jeu préalable du centre moteur controlatéral (Gastaut 1952). Sur l'hémisphère droit il se bloque après la contraction, traduisant l'effet désynchronisateur des afférences proprioceptives déclenchées par le mouvement.

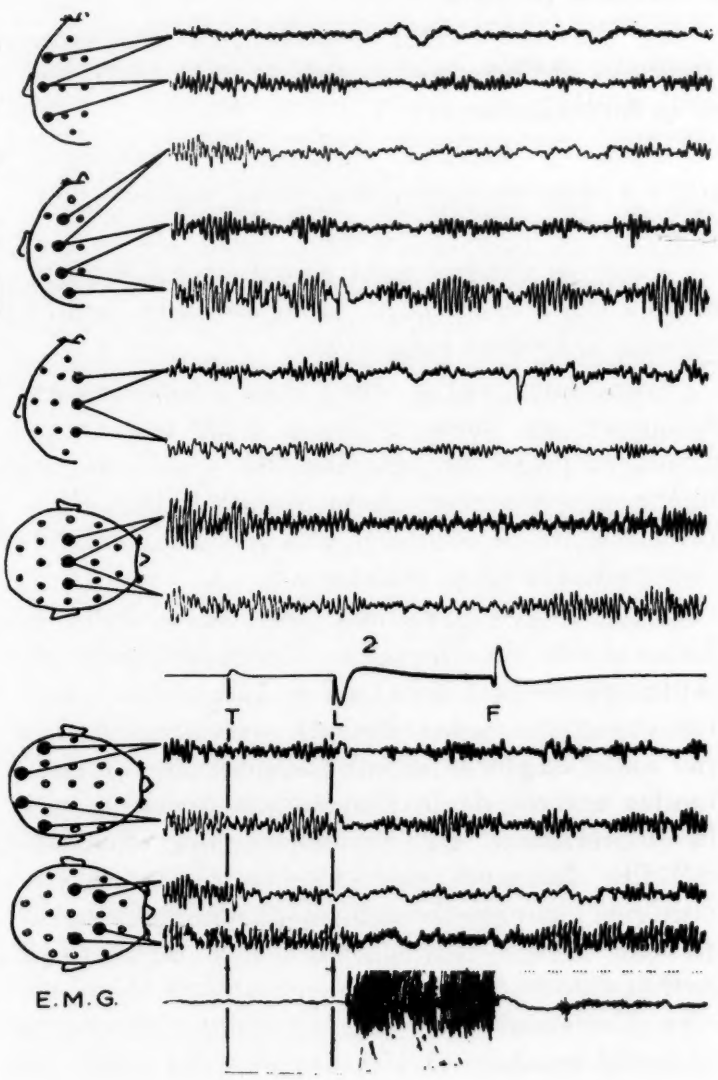


Fig. 1b

La deuxième combinaison provoque déjà une réaction conditionnée du rythme rolandique gauche qui se bloque dès l'introduction du son. (Cette réaction se voit très nettement sur la troisième et la treizième ligne qui enregistrent la dérivation fronto-rolandique gauche.) Toutes les réactions inconditionnées précédemment décrites se retrouvent après l'introduction de la lumière, à ceci près que la contraction du poing et le blocage rolandique droit qui en résulte sont plus précoces. Il n'existe pas encore de contraction musculaire conditionnée.

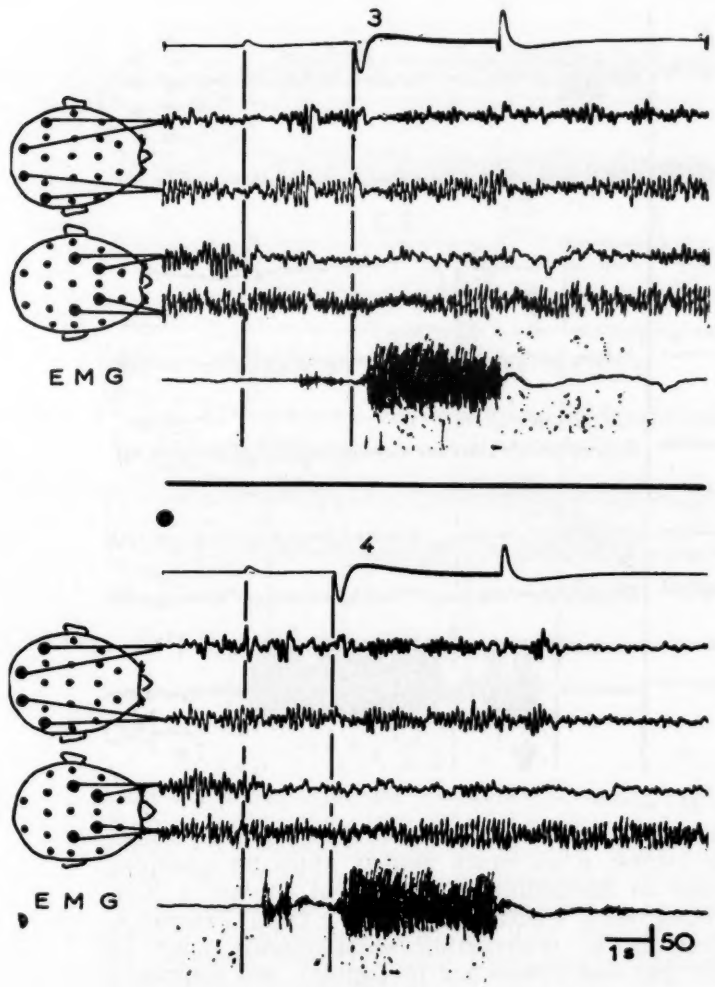
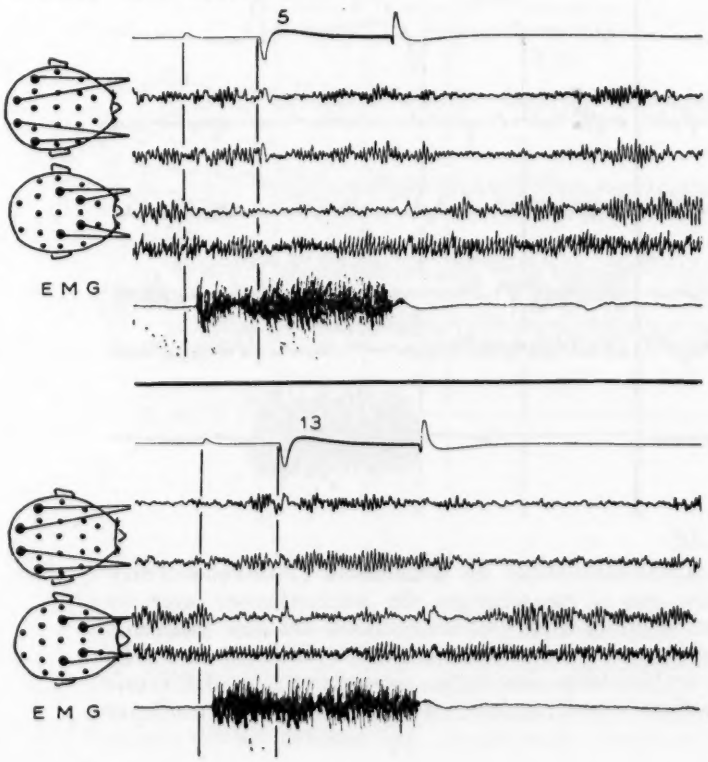


Fig. 1c

Développement progressif de la contraction musculaire conditionnée qui est à peine perceptible pour la troisième combinaison, mais beaucoup plus nette pour la quatrième. La réaction électroencéphalographique conditionnée demeure invariable sous la forme d'un blocage strictement localisé du rythme rolandique gauche. On remarque par contre l'atténuation progressive du blocage inconditionnel du rythme rolandique droit et du rythme occipital sous l'effet de l'habituation.



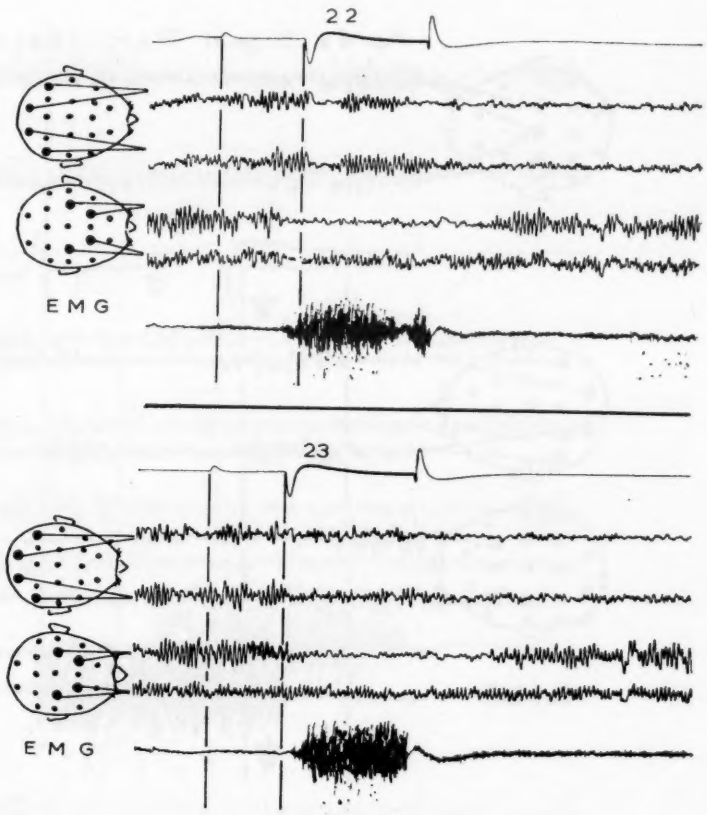


Fig. 1e

Epuisement spontané du conditionnement malgré le renforcement incessant du son par la lumière et par la contraction du poing. Alors que la 21ème combinaison avait donné une réaction conditionnée normale, on observe que la 22ème ne provoque plus qu'une petite contraction du poing juste avant le début de la lumière et que le blocage rolandique controlatéral est retardé de façon correspondante. Quant à la 23ème combinaison elle n'entraîne plus que la contraction inconditionnelle du poing et le blocage rolandique correspondant à l'exclusion de toute réaction conditionnée. Ce phénomène ne saurait être rattaché à l'extinction, puisque le stimulus conditionnel n'a cessé d'être renforcé. Nous croyons qu'il faut en faire l'expression du processus d'inhibition interne qui se développe sous l'effet de la répétition des stimulations (inhibition supramaximale de répétition).

Fig. 1d

Les mêmes phénomènes se répètent de façon identique et sans une seule exception de la 5ème à la 21ème combinaison (13ème combinaison choisie comme exemple).

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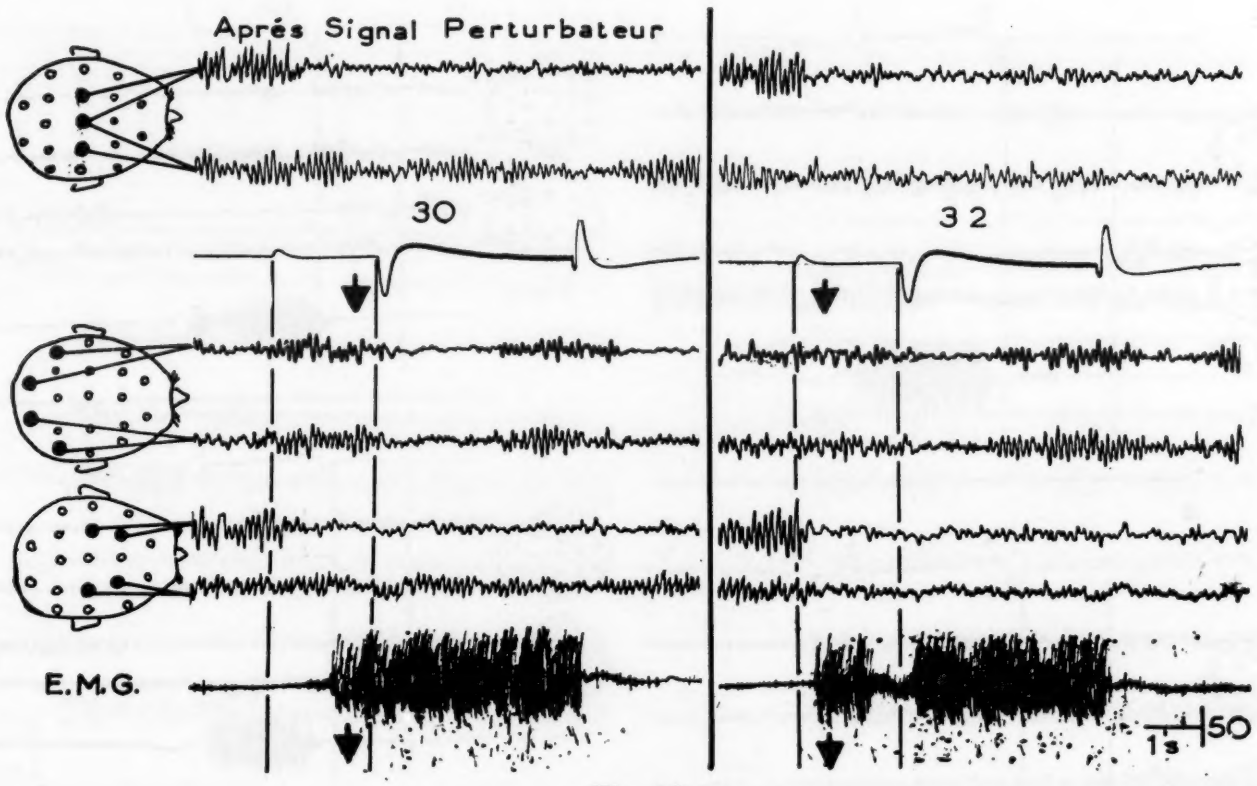

Fig. 1f

Réapparition de la réaction conditionnée qui était demeurée inhibée jusqu'à la 29ème combinaison, mais qui reparaît à la 30ème sous l'effet d'un bruit violent appliqué quelques secondes auparavant. Il s'agit là d'un phénomène de désinhibition sur lequel Pavlov a bien insisté, c'est-à-dire de l'inhibition d'une inhibition sous l'influence d'un « frein externe ». L'expérimentateur a profité de la réapparition de la contraction conditionnée pour la « surrenforcer » à l'aide du mot « Bien » (indiqué par une flèche sur la figure), qui approuve en quelque sorte l'anticipation de l'acte par rapport au signal lumineux. On « surrenforce » également les 6 combinaisons suivantes et, dès la 32ème, on observe que le blocage conditionné du rythme en arceau est devenu bilatéral et qu'il intéresse maintenant la région rolandique des deux hémisphères.

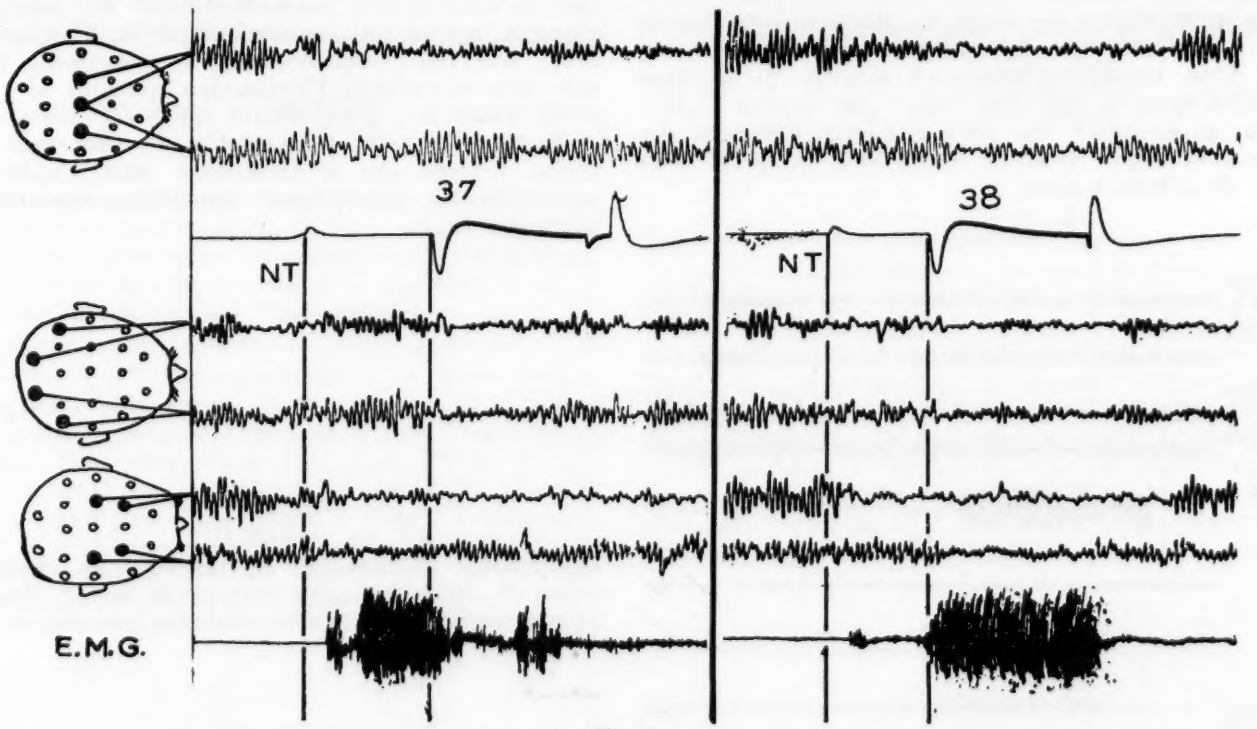

Fig. 1g

Les combinaisons 37 et 38 sont effectuées avec un son différent du précédent (Nouveau Ton) que l'on renforce toujours par la lumière mais que l'on néglige de surrenforcer par le mot « Bien ». On voit que le sujet n'effectue pas d'emblée la différenciation du son nouveau qui provoque la même réaction conditionnelle que le ton ancien surrenforcé (phénomène de la généralisation sensorielle de Pavlov). Dès la combinaison suivante cependant, la différenciation se manifeste par la perte de la contraction conditionnée et du blocage rolandique ipsilatéral.

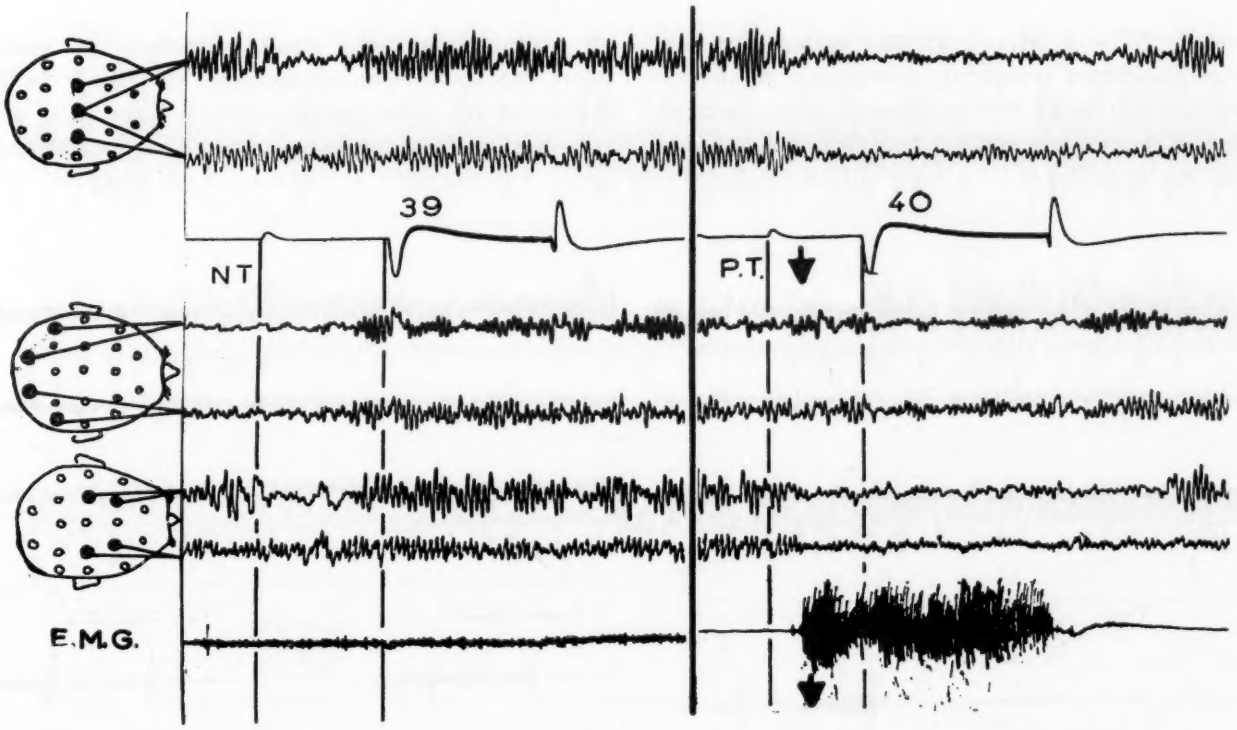

Fig. 1h

Lors de la combinaison suivante (39ème), l'inhibition de différenciation est tellement accrue que la contraction inconditionnée disparaît aussi et que le sujet ne serre même plus le poing à l'introduction de la lumière. Fait capital, ce phénomène d'inhibition motrice s'exprime sur l'EEG par une augmentation d'amplitude du rythme rolandique controlatéral. La 40ème combinaison, effectuée avec le ton ancien normalement surrenforcé (c'est-à-dire avec le stimulus conditionnel positif: Ton Positif), provoque évidemment la réaction conditionnée surrenforcée complète avec son blocage rolandique bilatéral. Il en sera de même pour les deux combinaisons suivantes.

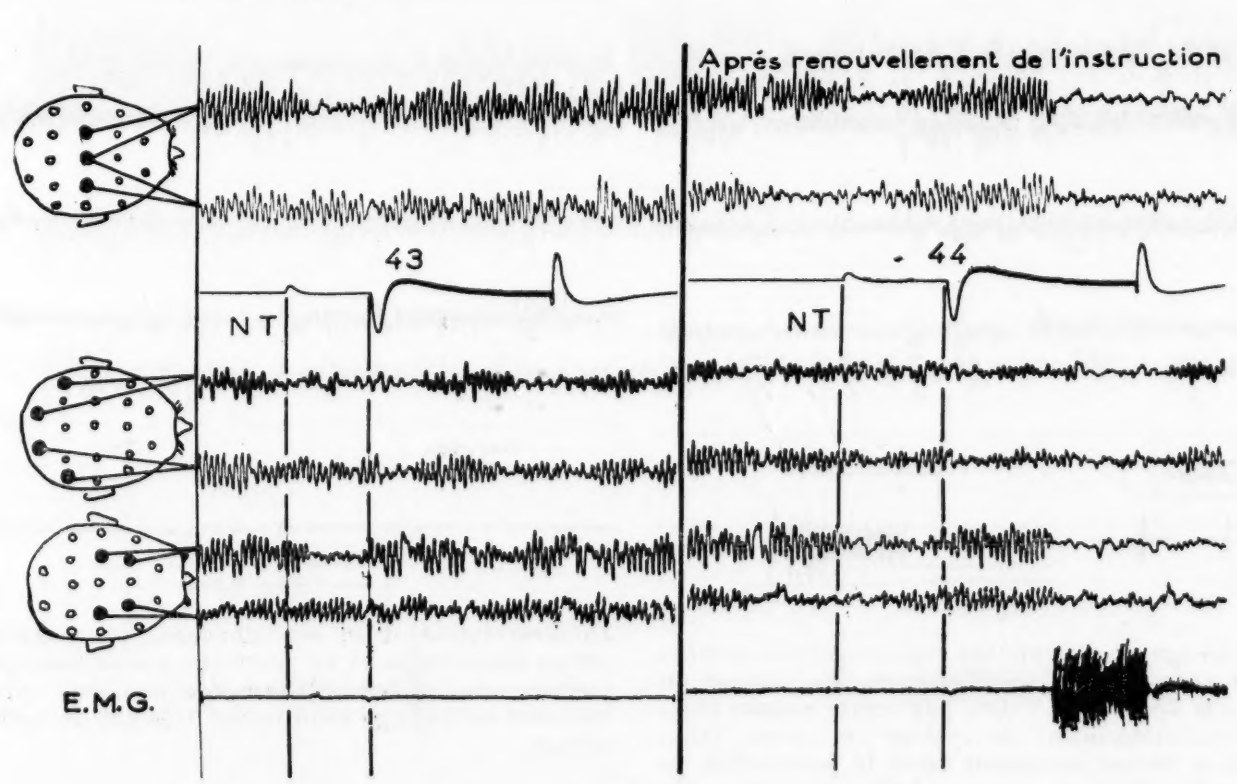

Fig. 1i

Persistance de l'inhibition de différenciation qui se manifeste de façon identique pour la 43ème combinaison effectuée avec le nouveau ton devenu signal négatif (Ton Négatif). La 44ème combinaison qui comporte le Ton Négatif, est appliquée après renouvellement de l'instruction: « il faut serrer le poing quand vous verrez la lumière »; on observe alors ce fait remarquable que le sujet présente quand même le renforcement du rythme rolandique controlatéral et que la contraction inconditionnelle ne survient qu'après la disparition brutale de ce rythme qui constituait l'expression indiscutable d'une inhibition locale.

Protocole II — J. M. . . ., 22 ans, épileptique psycho-moteur avec foyer temporal; lobectomie temporale antérieure droite; large brèche osseuse fronto-centro-temporale qui explique la grande amplitude du rythme en arceau rolandique droit. Pendant un enregistrement électroencéphalographique standard on le prie de serrer les deux poings chaque fois qu'il percevra une lumière à travers ses yeux fermés. (Fig. 2a à 2f)

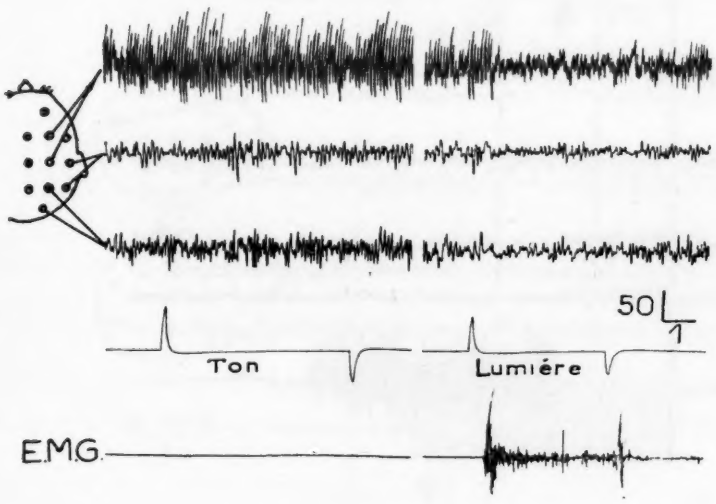

Fig. 2a

Inefficacité totale du son indifférent avant le conditionnement, tandis que la lumière provoque un blocage inconditionnel du rythme alpha occipito-pariéto-temporal et une contraction du poing qui déclenche à son tour le blocage inconditionnel du rythme en arceau.

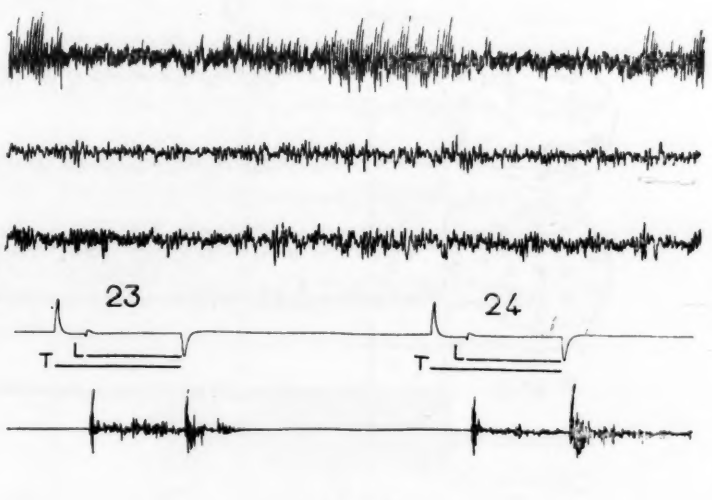

Fig. 2c

Blocage conditionné très net du rythme en arceau pour la 23ème et la 24ème combinaison, alors que le rythme alpha a complètement cessé de réagir au son aussi bien qu'à la lumière. Cette réaction conditionnelle est exclusivement corticale et ne s'accompagne d'aucune ébauche de contraction anticipée du poing; elle est apparue à la 15ème combinaison et demeure inchangée jusqu'à la 25ème.

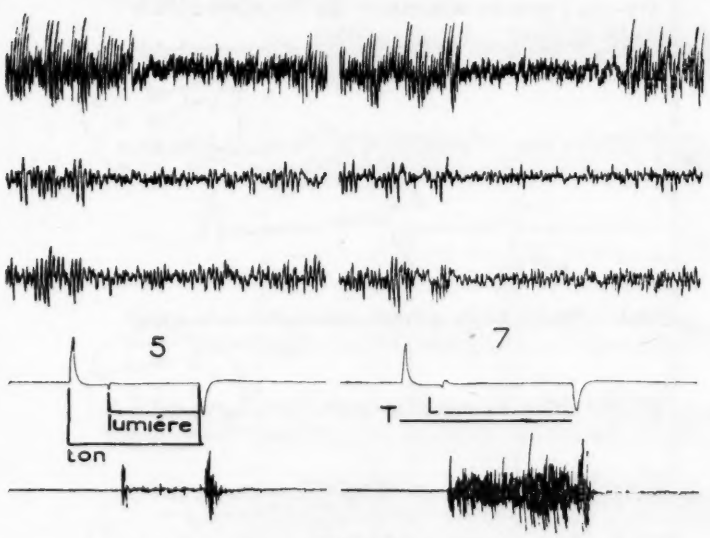

Fig. 2b

Discret blocage conditionné du rythme occipito-pariéto-temporal pour la 5ème combinaison, plus discret encore pour la 7ème. Il n'existe par contre aucune ébauche de conditionnement du rythme en arceau rolandique qui se bloque seulement après la contraction inconditionnelle du poing (sous l'effet des afférences proprioceptives centripètes qui en résultent).

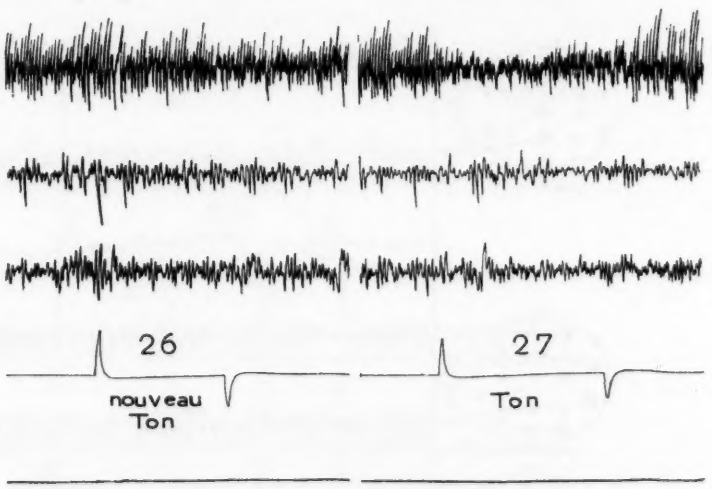

Fig. 2d

Différenciation d'un son nouveau qui constitue la 26ème stimulation et ne provoque aucun blocage alors que le son ancien (27ème combinaison) provoque toujours un blocage conditionné très net du rythme en arceau.

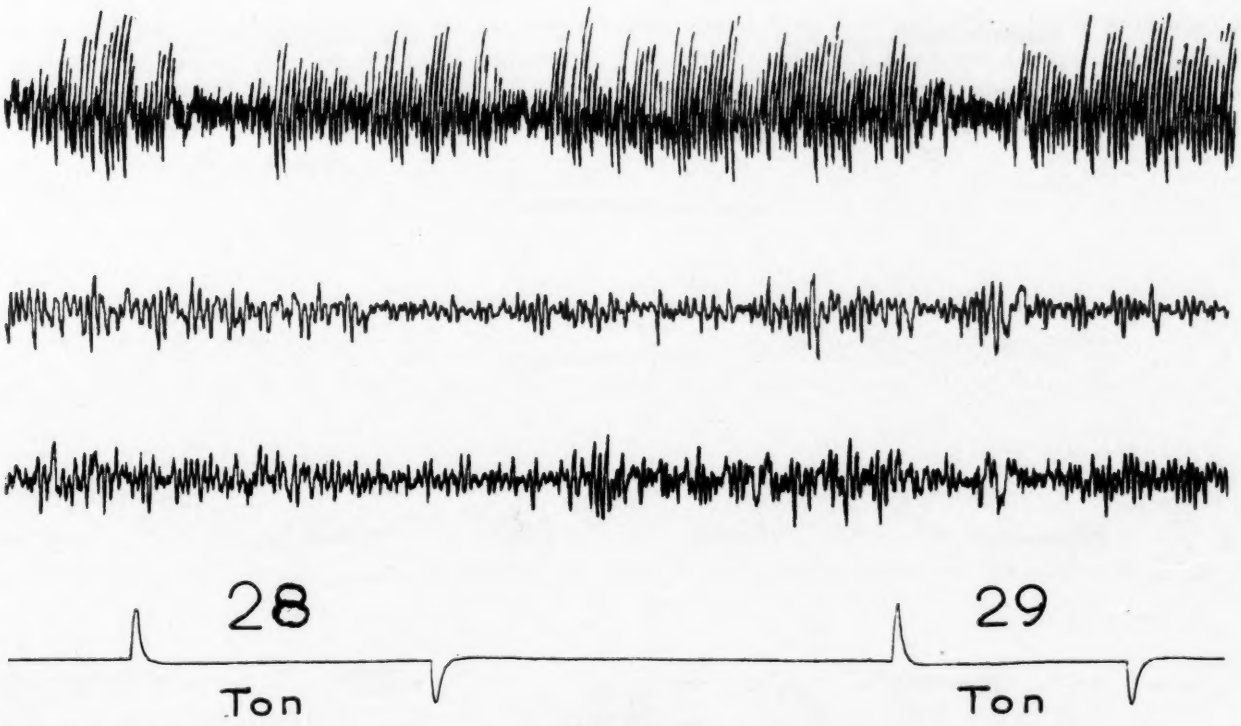

Fig. 2e

Extinction progressive du blocage conditionné rolandique sous l'effet du non-renforcement. La 27ème combinaison n'ayant pas été renforcée on voit que la 28ème stimulation ne produit qu'un léger blocage conditionnel. Cette dernière stimulation n'étant pas renforcée non plus, la 29ème stimulation provoque un blocage conditionnel plus discret encore.

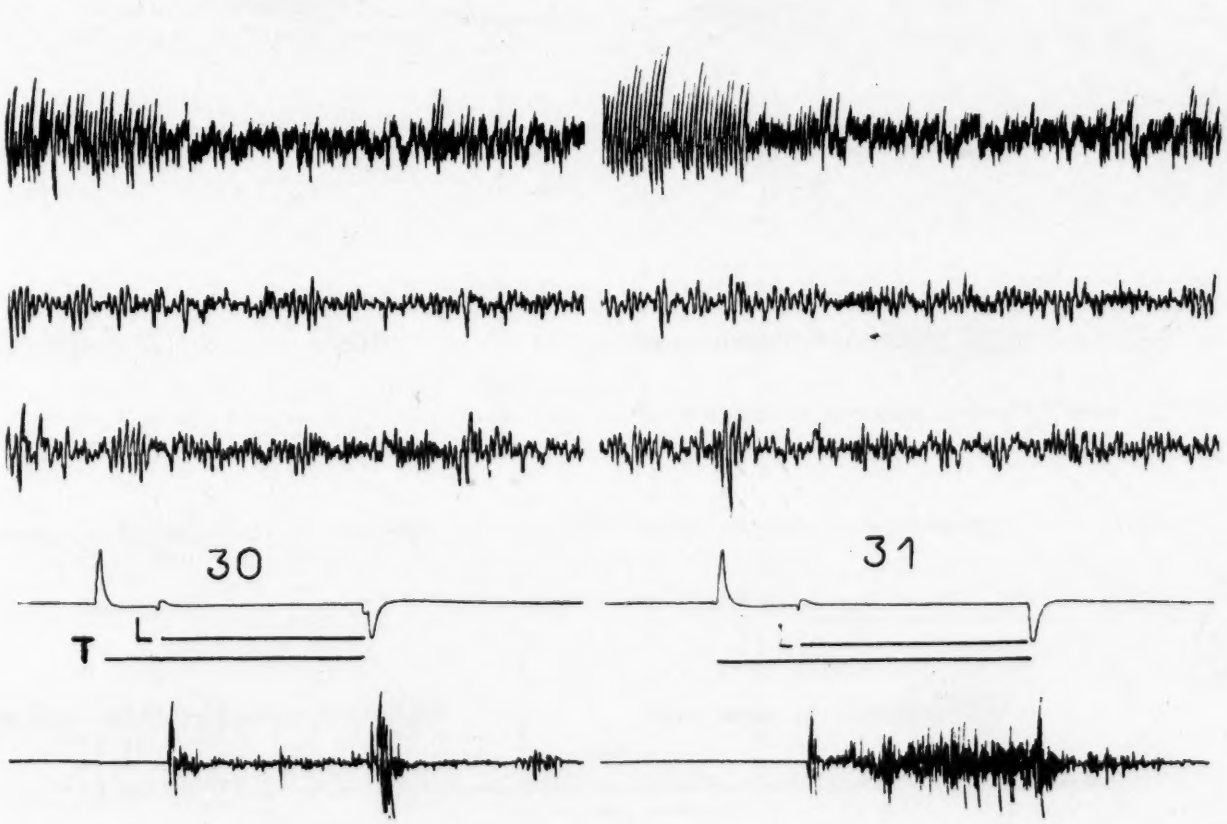

Fig. 2f

Absence complète de blocage conditionné pour la 30ème stimulation qui survient donc après 3 non-renforcements. Cette stimulation, par contre, est renforcée par la lumière et la contraction du poing. La 31ème combinaison montre que le blocage conditionné du rythme rolandique a été restauré par ce seul renforcement.

Protocole III — Ar..., 35 ans, sujet normal, est prié de serrer le poing chaque fois qu'il verra une lumière s'allumer devant ses yeux fermés.

Les différentes figures montrent les tracés primaires et l'analyse automatique de fréquences simultanée de 8 dérivations permettant l'étude du rythme alpha sur les régions occipitales, pariétales, temporales et même rolandiques. Ce sujet ne possède pas, en effet, de rythme en arceau indépendant mais il présente un rythme alpha très étendu. (Fig. 3a à 3e)

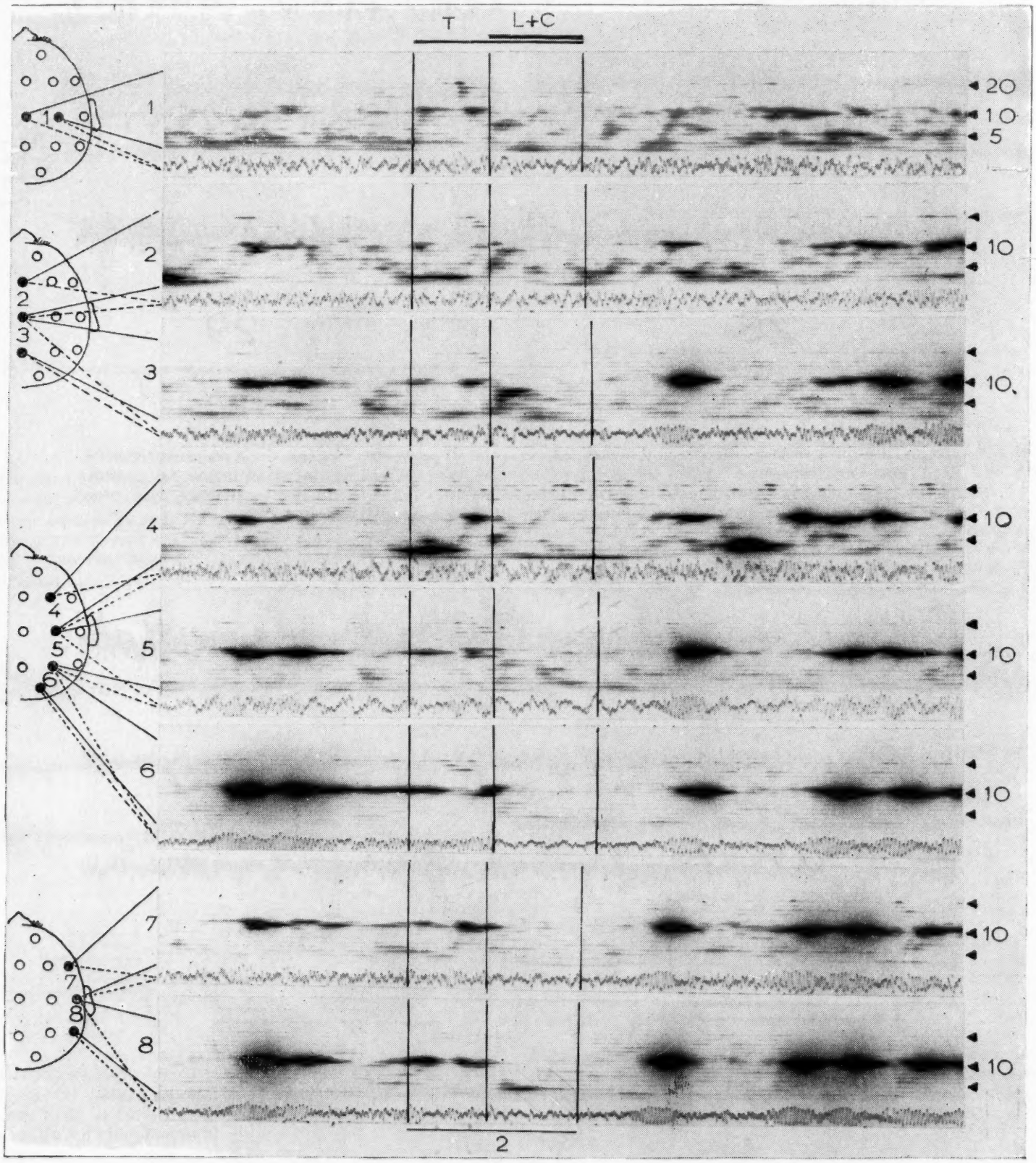

Fig. 3a

Existence d'un rythme alpha à 10 c/sec. réparti en bouffées fusiformes de grande amplitude sur les tracés primaires et représenté sur le spectrogramme par une bande noire d'intensité correspondante sur le canal enregistrant électivement la fréquence 10 c/sec. Ce rythme alpha est surtout important dans les dérivations occipitales, pariétales et temporales, mais il s'observe également dans la région rolandique. Il n'est pas bloqué par le son indifférent (T) qui est combiné pour la seconde fois à la lumière et à la contraction du poing (L + C) qui provoquent par contre une réaction d'arrêt généralisée. Il n'y a donc pas encore de réaction conditionnée sur l'électroencéphalogramme.

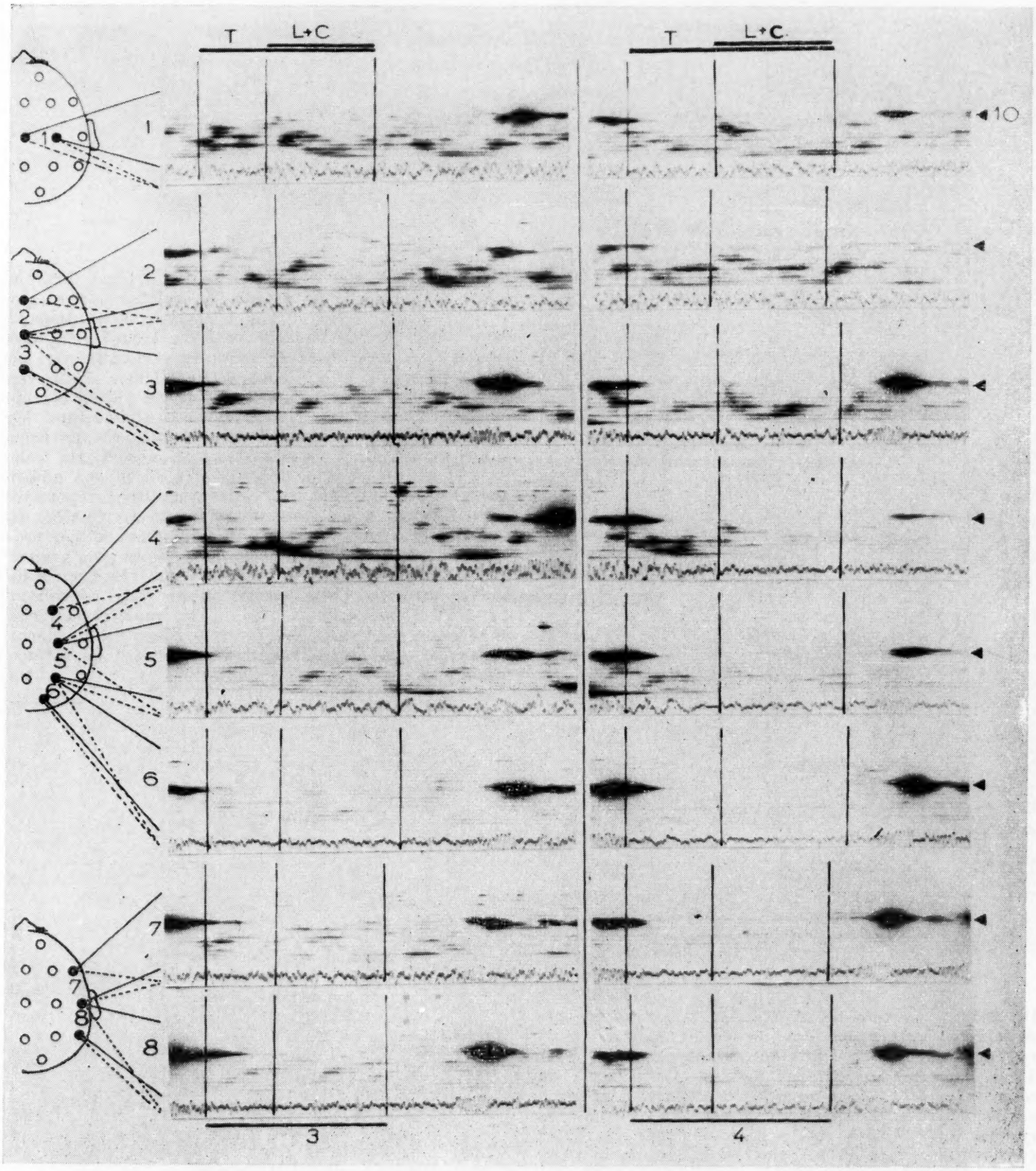

Fig. 3b

Le stimulus sonore provoque pour la 3ème et la 4ème combinaison un blocage généralisé du rythme alpha persistant pendant la lumière et la contraction du poing. La réaction électroencéphalographique conditionnée est donc acquise et elle se poursuivra jusqu'à la 6ème combinaison.

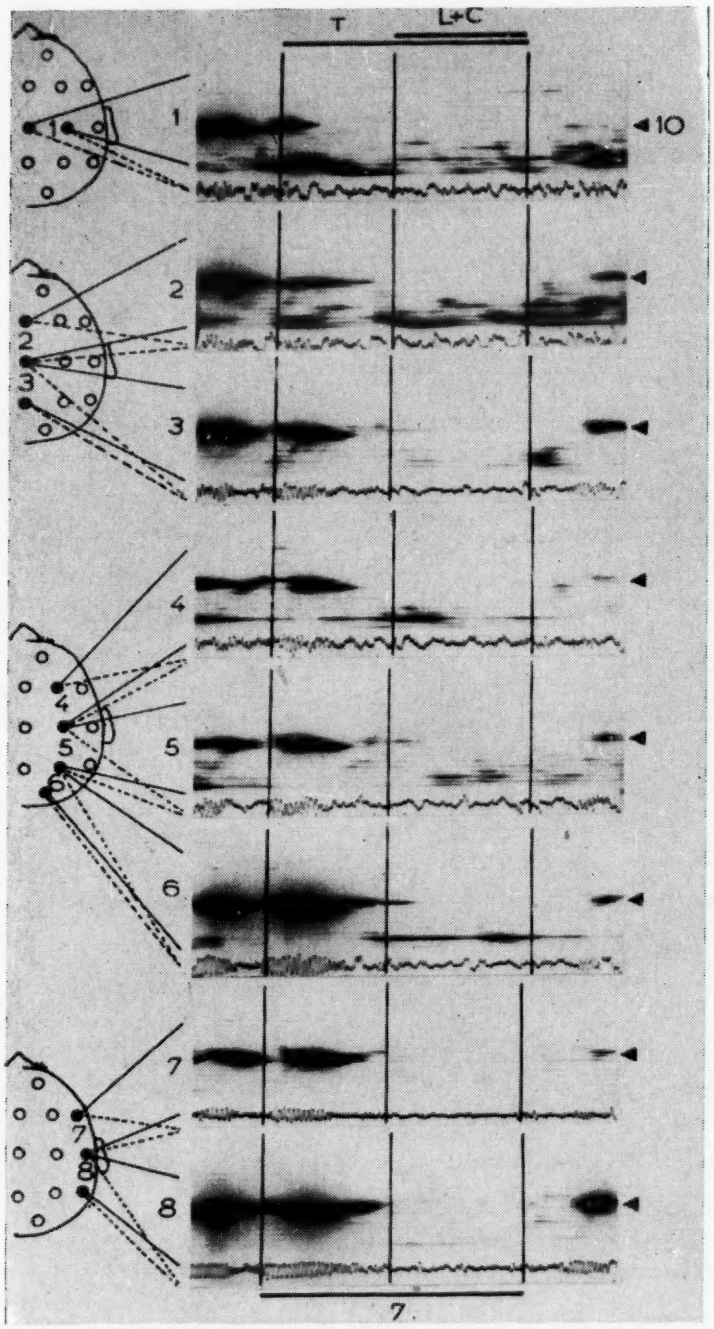

Fig. 3c

Disparition brutale de la réponse conditionnée lors de la 7ème combinaison dont le son ne modifie plus le rythme alpha qui continue de se bloquer sous l'effet de la lumière et de la contraction. Cette perte du conditionnement s'accompagne d'ailleurs d'un phénomène particulier: l'augmentation d'amplitude du rythme alpha qui se généralise sur tout le cortex (noter l'épaisseur de la bande noire sur le spectrogramme de toutes les régions analysées). Ce renforcement du rythme alpha qui rappelle celui du début de l'endormissement nous paraît être l'expression électroencéphalographique d'un processus d'inhibition interne généralisé à l'ensemble du cortex.

Fig. 3d

Un phénomène nouveau est apparu de façon brutale après la 9ème combinaison: le rythme alpha qui avait augmenté d'amplitude a soudainement disparu dans toutes les dérivations et s'est trouvé remplacé par des rythmes théta et delta très visibles sur les tracés primaires et sur les spectrogrammes. Dans ces conditions on observe que le son de la 12ème combinaison fait réapparaître le rythme alpha dans les régions temporo-occipitales seulement; réapparition qui répond à un processus d'excitation corticale localisée et à une véritable *réaction d'éveil* si l'on admet que le tracé lent dépourvu de rythme alpha répondait préalablement à un tracé de sommeil. La lumière et la contraction du poing qui accompagnent le son provoquent évidemment une excitation encore plus grande qui bloque à son tour le rythme alpha réapparu sous l'effet du son. Cette excitation ne dure cependant qu'une seconde après la fin de la lumière puis elle se laisse rapidement submerger par l'inhibition interne croissante qui fait d'abord réapparaître le rythme alpha puis les tracés de sommeil.

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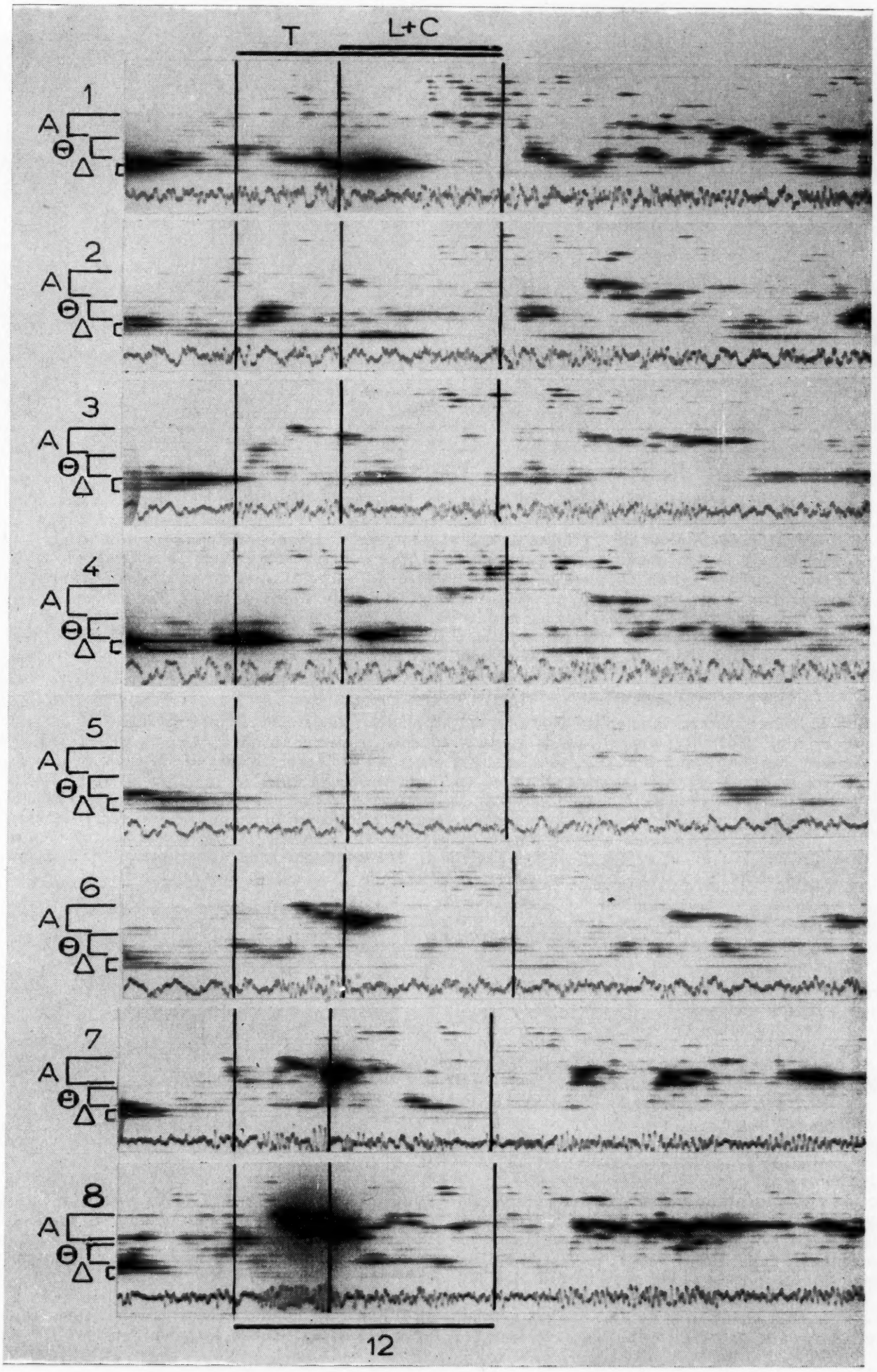
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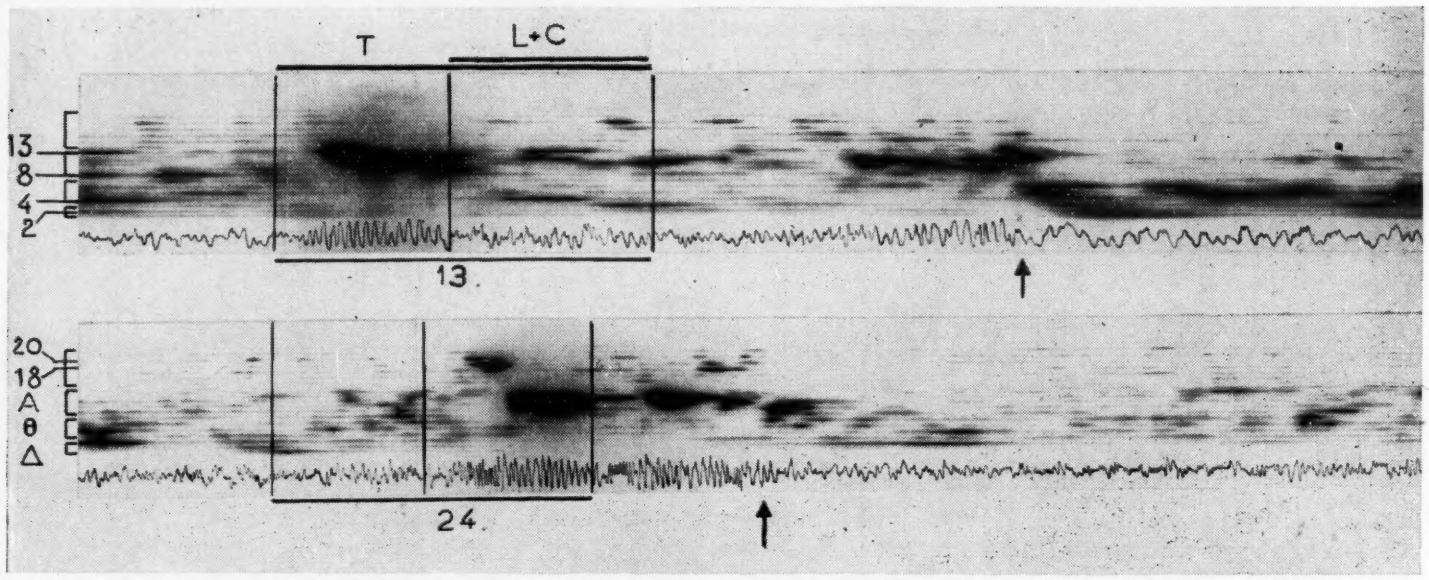

Fig. 3e

Succession des mêmes phénomènes au cours de la 13ème stimulation, appliquée alors que les tracés sont caractéristiques d'un sommeil électrique léger (absence du rythme alpha à 10 c/sec. et prédominance de rythmes à 4, 8 et 13 c/sec.). On observe la « réaction d'éveil » provoquée par le son conditionnel (apparition d'une bouffée très ample d'activité alpha à 10 c/sec.) et la réaction de blocage par la lumière du rythme alpha nouvellement réapparu. Après la fin de la stimulation on voit persister pendant 2 secondes la désynchronisation qui traduit un processus d'excitation résiduelle, puis on voit réapparaître le processus d'inhibition interne généralisée qui se manifeste d'abord par la réapparition du rythme alpha puis par sa disparition et son remplacement par des ondes lentes. Ce dernier phénomène, indiqué par une flèche, est tellement brutal qu'on pourrait l'opposer à la réaction d'éveil et en faire une véritable réaction d'assoupissement.[1]

Sur la même figure la combinaison 24 est appliquée alors que le sommeil électrique est encore plus profond (disparition de toute fréquence appartenant à la bande alpha, prédominance des rythmes à 3 et 5 c/sec.). L'inhibition est cette fois tellement importante que le son conditionnel est devenu sans effet et qu'il ne provoque plus la réaction d'éveil. Cette dernière survient seulement sous l'effet de la lumière qui fait réapparaître le rythme alpha à 10 c/sec.[2] en même temps qu'elle provoque encore la contraction du poing suivant l'instruction préalable. Le rythme alpha persiste naturellement pendant la brève période d'excitation qui succède au stimulus inconditionnel et il disparaît brutalement (flèche) au moment où le processus d'excitation est submergé par celui de l'inhibition interne.

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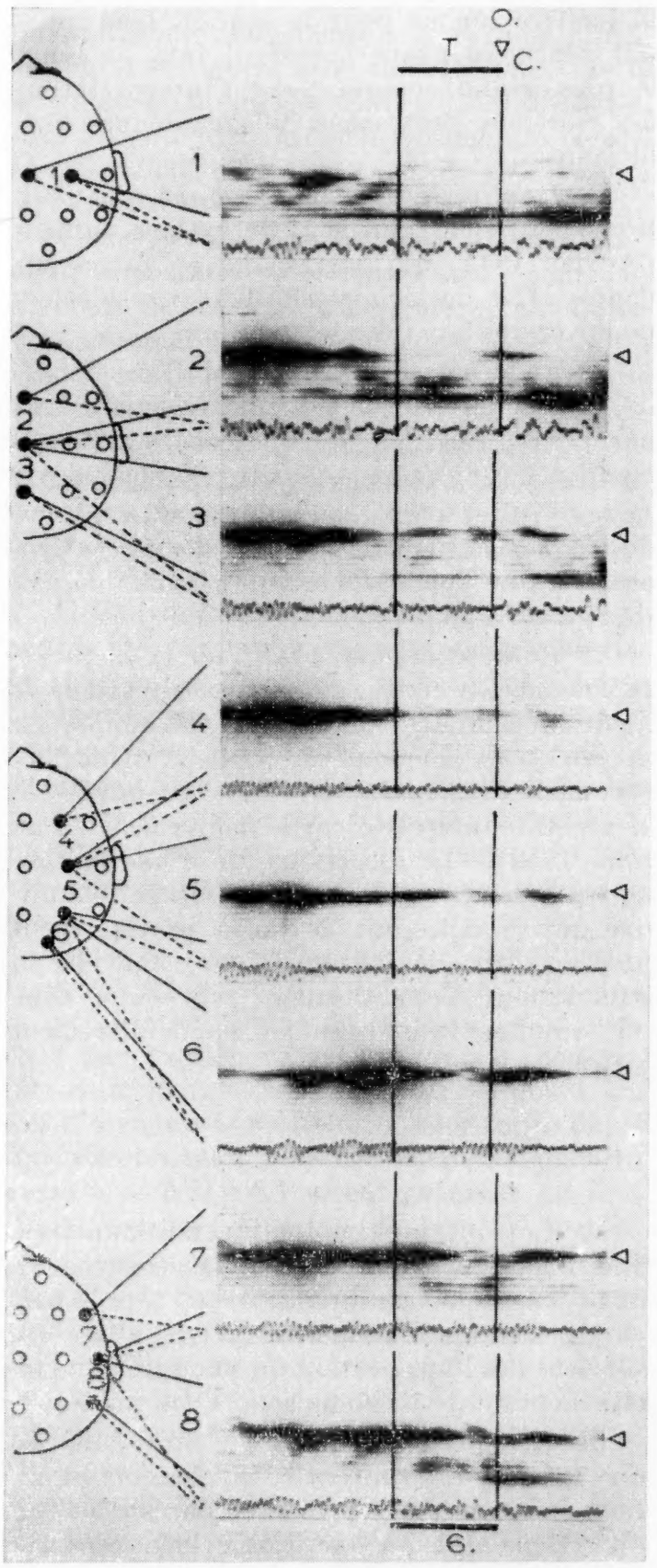
[1] Il est intéressant de remarquer que la réapparition du rythme alpha dans la réaction d'éveil et la réapparition des rythmes lents dans la réaction d'assoupissement se fait d'une façon très particulière, les fréquences les plus rapides apparaissant les premières. L'un de nous (Storm van Leeuwen) a montré que ce phénomène tient au fait que ces rythmes réapparaissent dans une région limitée avec leur fréquence la plus élevée et qu'ils s'étendent ensuite autour de cette région en diminuant de fréquence.

[2] Cette réaction d'éveil est plus complexe que les précédentes dans la mesure où la réapparition du rythme alpha à 10 c/sec. est annoncée par l'apparition d'une brève bouffée de rythme bêta à 20, 18, 16 c/sec. dont les fréquences les plus rapides apparaissent également les premières.



Protocole IV — Sujet du Protocole III, enregistré dans d'autres circonstances. On ne fournit cette fois aucune instruction préalable, l'ordre de serrer les poings étant donné verbalement deux secondes après la présentation d'un son indifférent (T = son; O = ordre; C = contraction).

Ici le stimulus inconditionnel est représenté par la seule volée proprioceptive corticipete accompagnant la contraction du poing. (Fig. 4)

Fig. 4

Le son de la 6ème combinaison provoque le blocage conditionné du rythme alpha dans la région rolandique (dérivation 1, 2 et accessoirement 4) alors qu'il est absolument sans effet sur le rythme des régions occipito-parieto-temporales. (Rappelons en effet que ce sujet qui ne présente pas de rythme en arceau indépendant possède cependant une activité rolandique sous la forme du rythme alpha qui s'étend largement sur cette région).

Ce blocage localisé qui s'est maintenu très longtemps sans accompagnement réflexo-conditionné moteur (c'est-à-dire sans que survienne la contraction anticipée des poings) montre bien que les réactions électroencéphalographiques conditionnées dépendent du territoire mis en jeu par le stimulus inconditionnel et non du caractère morphologique des activités qui occupent ce territoire. Ce n'est pas le rythme en arceau qui est localement conditionné, ce sont toutes les activités électriques qui occupent la région rolandique, qu'il s'agisse d'un rythme en arceau, d'un rythme bêta ou d'un rythme alpha anormalement étendue en avant.

III — ÉTUDE ÉLECTROENCÉPHALOGRAPHIQUE DU PROCESSUS D'EXCITATION CENTRALE AU COURS DU CONDITIONNEMENT

Les observations que nous venons de rapporter confirment celles de nos prédécesseurs d'après qui l'excitation conditionnée s'exprime par un blocage transitoire du rythme cortical; toutefois nos observations montrent au surplus que ce blocage ne concerne pas le seul rythme alpha dans son ensemble, mais qu'il peut intéresser de façon concomitante ou indépendante le rythme rolandique de l'un ou l'autre hémisphère suivant le type de stimulus absolu utilisé.

Autrement dit, nous arrivons à la conclusion que le processus d'excitation corticale conditionnée se concentre dans une région correspondant plus ou moins à celle de l'analyseur inconditionnel. C'est ce processus de concentration de l'excitation que nous allons étudier après avoir envisagé l'effet électroencéphalographique des stimuli indifférents et absolus.

1° *Modifications « inconditionnées » de l'EEG sous l'effet du stimulus INDIFFÉRENT avant le conditionnement.*

Nous avons utilisé dans toutes nos expériences une seule variété de stimulus indifférent, représenté par un son peu intense supposé sans effet sur l'EEG. L'« indifférence » de notre stimulus par rapport à l'EEG n'est cependant pas acquise d'emblée et le sujet présente un blocage plus ou moins important mais généralisé de ses rythmes corticaux (alpha et arceau) la première fois qu'on lui fait entendre le son. Cet effet s'atténue cependant très rapidement et le son devient effectivement indifférent après 2 à 6 répétitions (« habituation »).

2° *Modifications « inconditionnées » de l'EEG sous l'effet du stimulus ABSOLU avant le conditionnement.*

Cet effet varie évidemment suivant la nature du stimulus utilisé:

A. *La stimulation lumineuse continue* provoque le blocage généralisé du rythme alpha connu sous le nom de « réaction d'arrêt », dont l'importance diminue lors des stimulations ultérieures qui peuvent même devenir inefficaces si elles sont trop souvent répétées. Il existe donc un processus d'habituation pour la lumière comme pour le son, et, bien qu'il soit beaucoup moins accusé, il faut en tenir le plus grand compte pour l'interprétation des réactions électroencéphalographiques conditionnées.

B. *La stimulation lumineuse intermittente* provoque l'« entraînement du rythme alpha » (Adrian 1941) qui correspond en fait à un double effet des éclairs sur l'activité bioélectrique occipito-pariéto-temporale:

a) un blocage du rythme alpha;

b) l'apparition de potentiels évoqués à la même fréquence que les éclairs stimulateurs.

Ces deux phénomènes sont indépendants (Grey Walter 1949) et l'analyse automatique de fréquences montre que certains sujets présentent des potentiels évoqués sans blocage du rythme alpha.

C. *Le déplacement passif de la main ou sa contraction active,* agissent électivement et identiquement sur le rythme rolandique en arceau qu'ils bloquent sur les deux hémisphères mais principalement du côté opposé à l'extrémité intéressée par le mouvement (Gastaut 1952). Le processus de l'habituation agit peu sur cette réaction de blocage rolandique qui se reproduit de façon pratiquement identique chaque fois que l'on renouvelle la stimulation. Cette dernière représente donc un stimulus inconditionnel particulièrement efficace.

3° *Modifications « conditionnées » de l'EEG lorsque le stimulus indifférent est combiné à un stimulus absolu UNIQUE.*

A. Lorsque le stimulus inconditionnel est une *lumière continue,* la réaction électroencéphalographique conditionnée est représentée par le classique blocage du rythme alpha qui survient dès l'application du son après un certain nombre de combinaisons « son-lumière ».

B. Lorsque le stimulus inconditionnel est une *lumière intermittente,* la réaction conditionnée est encore représentée par un blocage du rythme alpha, à condition évidemment que le stimulus lumineux intermittent provoque ce blocage de façon inconditionnelle.

Autrement dit, la stimulation lumineuse intermittente ne provoque de réactions conditionnées que dans la mesure où elle agit com-

me la stimulation lumineuse continue, en bloquant inconditionnellement le rythme alpha. A l'inverse, l'autre effet inconditionnel de la stimulation lumineuse intermittente, c'est-à-dire les potentiels évoqués rythmiques constituant « l'entraînement » d'Adrian, n'a pu être conditionné avec notre technique.

Cette donnée négative nous a paru tellement importante que nous l'avons contrôlée au cours de 35 expériences comportant l'analyse automatique de fréquences des cas où l'existence d'un « entraînement » conditionné semblait discutable sur les tracés primaires. Dans aucun de ces cas nous n'avons pu trouver la moindre ébauche de cet entraînement conditionné, qui a cependant été obtenu par Morrel et Jasper 1955, Morrel et Naquet 1956, Yoshii, Pruvot et Gastaut 1956, chez l'animal.

C. Lorsque le stimulus inconditionnel est représenté par *le déplacement de la main ou la contraction du poing,* la réaction électroencéphalographique conditionnée n'intéresse plus le rythme alpha mais seulement le rythme en arceau rolandique qui se bloque sur l'hémisphère controlatéral. Ce blocage conditionné est généralement obtenu de façon très précoce, dès la deuxième ou troisième combinaison.

Dans le cas particulier du conditionnement verbal-moteur d'Ivanov Smolenski (où la mobilisation active de la main est déclenchée par l'ordre verbal « serrez le poing », introduit deux secondes après le début du son), on observe que le blocage conditionné du rythme rolandique controlatéral survient avant le réflexe conditionné moteur.

La « précession » du phénomène cortical varie beaucoup d'un sujet à l'autre. Elle peut être brève, précédant d'une combinaison seulement la contraction conditionnée du poing. Elle peut être très longue et la contraction conditionnée peut même ne jamais survenir, tandis que le blocage cortical conditionné a été très précoce.

Le conditionnement verbal-moteur d'Ivanov Smolenski permet d'effectuer un renforcement verbal de la contraction conditionnée du poing. Pour cela il suffit de prononcer le mot « Bien » dès que le sujet a serré la main en entendant le son; ce qui constitue en fait une approbation pour avoir anticipé l'ordre et un encouragement à continuer. Dans ces conditions, on peut voir apparaître un phénomène cortical nouveau: la bilatéralisation du blocage rolandique conditionné.

4° *Modifications « conditionnées » de l'électroencéphalogramme lorsque le stimulus indifférent est combiné à des stimuli absolus MULTIPLES.*

Nous rappellerons que les conditions expérimentales sont celles du conditionnement classique son-lumière, mais que le sujet a reçu l'instruction préalable de serrer le poing droit quand il perçoit la lumière. Dans ces conditions le stimulus inconditionnel est double, puisqu'il comporte les afférences visuelles qui vont bloquer le rythme alpha des deux côtés et les afférences proprioceptives qui vont bloquer le rythme rolandique du côté opposé au poing qui se contracte.

La réaction électroencéphalographique conditionnée peut ici revêtir deux aspects topographiques différents: ou bien elle bloque simultanément le rythme alpha des deux hémisphères et le rythme en arceau rolandique controlatéral, ou bien elle intéresse seulement ce dernier. Dans le premier cas, le blocage conditionné du rythme alpha est d'ailleurs très labile; il s'atténue et disparaît rapidement, laissant persister uniquement le blocage du rythme rolandique controlatéral qui représente donc l'élément essentiel de la réaction électroencéphalographique (cf. protocole II).

Lorsqu'il existe et quand il persiste, le blocage conditionné du rythme alpha est souvent remarquable par son asymétrie du fait de sa prédominance sur l'hémisphère où se bloque conditionnellement le rythme en arceau, c'est-à-dire du côté opposé au poing qui se contracte.

Quelle que soit sa topographie, cette réaction électroencéphalographique conditionnée est encore remarquable par sa « précocité » (2ème ou 3ème combinaison dans la plupart des cas) et par le fait qu'elle précède toujours la contraction conditionnée du poing.

Le conditionnement périphérique peut être rapidement obtenu (protocole I) ou au contraire ne jamais survenir (protocole II). Lorsque il survient on peut évidemment le renforcer par le mot « Bien » et on observe alors la bilatéralisation du blocage rolandique

conditionné que nous avons déjà signalée à propos du procédé d'Ivanov Smolenski.

5° *Interprétation des réactions électroencéphalographiques conditionnées, à la lumière des théories Pavloviennes sur le processus de l'excitation centrale.*

Ayant admis, au début de ce travail, que l'EEG constituait un moyen d'approche direct des phénomènes conditionnés, nous devons maintenant confronter nos données avec celles de la réflexologie Pavlovienne. Cette dernière admet, en effet, l'existence d'un double processus d'excitation localisé autour des analyseurs corticaux des stimuli conditionnels et inconditionnels; processus d'excitation dont la mobilité dans l'espace et dans le temps doit permettre les « liaisons temporaires » nécessaires à l'élaboration des réflexes conditionnés.

A. L'existence d'un équivalent électroencéphalographique du processus d'excitation centrale ne fait aucun doute puisque nous l'avons retrouvé dans chacune de nos expériences et toujours sous la forme d'un blocage du rythme fondamental de la région envisagée. Il est remarquable que ce processus d'excitation corticale suspecté par Pavlov et dont il affirmait le caractère unique s'exprime justement par un seul phénomène bioélectrique: le blocage actif de l'autorythmicité neuronique locale que les électrophysiologistes considèrent justement comme l'expression de l'excitation corticale. Nous avons vu à ce propos que le processus d'excitation corticale conditionnée ne peut revêtir chez l'homme l'aspect d'un rythme nouveau respectant la fréquence d'un stimulus inconditionnel rythmique; résultat négatif qui témoigne du caractère non spécifique que revêt le processus d'excitation corticale conditionnée chez l'homme.

B. Du point de vue de l'évolution temporelle du processus d'excitation centrale, il apparaît d'abord que la réaction de blocage conditionné du rythme rolandique controlatéral est un précurseur de la contraction conditionnée du poing; c'est-à-dire qu'elle correspond à une représentation corticale préalable de l'acte de serrer le poing ou, plus simplement, à une mise en tension préalable de la région rolandique où l'acte moteur sera ultérieurement élaboré. Une telle supposition est fortement étayée par le fait (fig. 1a) que la contraction volontaire inconditionnelle du poing est toujours précédée d'un blocage du rythme en arceau controlatéral impliquant l'excitation préalable du cortex somato-moteur. L'observation faite par Jasper et Penfield 1949, Gastaut 1952, et Magnus 1954, selon laquelle la représentation mentale d'un acte moteur suffit à provoquer le blocage du rythme rolandique controlatéral est encore un argument en faveur de cette supposition.

Nous croyons devoir insister, enfin, sur la précocité des réactions de blocage conditionné qui surviennent souvent dès les premières combinaisons. Il nous semble possible que la plasticité et la versatilité du comportement humain dépendent, en partie au moins, de la grande rapidité de formation des foyers d'excitation conditionnée corticale.

C. Du point de vue de l'évolution spatiale, il nous est apparu que les manifestations électroencéphalographiques du processus d'excitation conditionnée n'étaient pas généralisées à l'ensemble du cortex, mais localisées à un territoire variable suivant le stimulus *inconditionnel* utilisé.

a) Il est d'ailleurs logique de penser que la nature du stimulus *conditionnel* ne peut jouer aucun rôle dans la localisation du blocage conditionné, puisque ne deviennent conditionnels que des stimuli préalablement rendus indifférents.

Malgré cela, pour contrôler cette assertion, nous avons utilisé chez 5 sujets le conditionnement verbal-moteur d'Ivanov Smolenski en remplaçant le son conditionnel par une lumière très faible dont l'effet de blocage sur le rythme alpha était vite épuisé. Nous avons néanmoins noté un blocage conditionné du rythme en arceau controlatéral identique à celui obtenu avec un stimulus sonore.

Une dernière preuve est fournie par l'analyse automatique de fréquences simultanée des régions occipitales et temporales qui ne nous a jamais montré de différence que le stimulus conditionnel soit lumineux ou auditif.

Nous admettons donc que le stimulus conditionnel, choisi pour son indifférence préalable envers l'EEG, ne joue aucun rôle

dans la localisation du blocage cortical conditionné. Opinion qui ne préjuge évidemment pas des résultats susceptibles d'être obtenus dans d'autres conditions expérimentales, notamment dans celles qui utiliseraient un stimulus conditionnel non indifférent sur l'EEG.

b) La nature du stimulus *inconditionnel* joue au contraire le rôle capital dans la localisation du processus d'excitation conditionnée et nous avons vu que le territoire du blocage conditionné est exactement le même que celui du blocage inconditionné (c'est-à-dire celui du rythme alpha occipito-parieto-temporal pour les stimuli lumineux et celui du rythme rolandique controlatéral pour les stimuli somesthésiques).

Autrement dit, nous arrivons à la conclusion qu'il n'existe qu'un seul foyer d'excitation, siégeant autour de l'analyseur inconditionnel, lors du conditionnement électrocortical. Conclusion qui ne s'accorde pas avec le schéma théorique admis par l'école Pavlovienne, suivant laquelle il existerait deux foyers, l'un conditionnel, l'autre inconditionnel, à partir desquels l'excitation irradierait sous la forme de deux trains d'ondes, dont la rencontre rendrait possible la liaison temporaire des deux foyers corticaux. Nous reviendrons sur cette discordance dans le dernier chapitre réservé à l'étude neurophysiologique.

c) Il est intéressant de remarquer que l'utilisation *indépendante* d'un stimulus inconditionnel lumineux ou somesthésique, provoque un blocage conditionné stable du rythme alpha ou du rythme rolandique, tandis que l'utilisation *simultanée* de ces deux stimuli n'entraîne qu'un blocage conditionné transitoire du rythme alpha et conditionne au contraire de façon stable le rythme en arceau. Nous avons même vu que cette prédominance des stimuli inconditionnels somesthésiques peut être telle qu'elle neutralise d'emblée l'effet du stimulus visuel et qu'elle provoque alors directement un blocage conditionné rolandique isolé.

Sans vouloir expliquer de tels faits nous pensons qu'ils peuvent être considérés comme l'équivalent électroencéphalographique d'un processus de « dominance » (Oukhtomski). Si l'on acceptait cette analogie il faudrait alors admettre que la mission de serrer le poing à un signal donné, qui met en jeu le deuxième système de signalisation et tout un apprentissage conditionnel réalisé pendant le développement ontogénique, représente un signal doué d'une signification biologique beaucoup plus importante que celle liée au simple éclairement passif de la rétine.

Ce signal somesthésique biologiquement significatif provoquerait un foyer d'excitation rolandique intense (foyer dominant) capable d'attirer vers lui toutes les impulsions corticipètes destinées à d'autres analyseurs, ce qui expliquerait l'absence ou la disparition du blocage alpha tandis que persiste le blocage du rythme en arceau rolandique.[1]

Il est bien évident qu'il ne s'agit là que d'hypothèses dépourvues de tout fondement objectif ; nous n'accordons donc aucune valeur explicative aux données fournies dans ce paragraphe dont le principal but a été de montrer dans quelle mesure nos constatations électroencéphalographiques correspondent aux principes théoriques de la réflexologie Pavlovienne.

IV — ÉTUDE ÉLECTROENCÉPHALOGRAPHIQUE DU PROCESSUS D'INHIBITION CENTRALE AU COURS DU CONDITIONNEMENT

Le but de ce chapitre est d'étudier la topographie et la chronologie des manifestations électroencéphalographiques de l'inhibition centrale. Suivant la classification de Pavlov (Grande Encyclopédie Médicale Russe, 1934) nous distinguerons :

1° une inhibition conditionnelle, interne ou active, comprenant les inhibitions de l'extinction, de la différenciation et du retard,

2° une inhibition inconditionnelle, comprenant l'inhibition externe et l'inhibition supramaximale (ou supra-liminaire).

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[1] Si l'on accepte d'identifier le blocage rolandique controlatéral à un foyer dominant au sens d'Oukhtomski, on peut poursuivre le raisonnement par analogie et admettre :

1°) que la prédominance controlatérale du blocage du rythme alpha observée chez certains sujets exprime cette dominance (irradiation de l'excitation rolandique dominante à tout l'hémisphère et notamment aux régions occipito-parieto-temporales) ;

2°) que le blocage rolandique bilatéral observé lors du renforcement verbal de l'acte moteur réflexo-conditionné traduit également cette dominance (ce renforcement augmenterait l'excitation rolandique qui par voie commissurale irradierait à la région homologue du côté opposé).

1° *Etude électroencéphalographique de l'inhibition interne.*

L'inhibition d'extinction survient, d'après Pavlov, lorsqu'on néglige de renforcer plusieurs fois de suite le stimulus conditionnel par le stimulus inconditionnel et se traduit par la cessation momentanée du réflexe conditionné.

Dans nos expériences il a toujours suffi de négliger plusieurs fois de suite le renforcement du stimulus conditionnel, pour voir disparaître le blocage conditionné. Quelquefois même, il a suffi d'un seul non-renforcement pour aboutir à ce résultat (cf. protocole II).

L'inhibition de différenciation apparaît classiquement lorsqu'on introduit un stimulus nouveau non renforcé (dit stimulus négatif) qui ne provoque pas le réflexe conditionné, tandis que le signal conditionnel renforcé (dit positif) le provoque toujours.

Dans nos expériences, l'application d'un son nouveau peu différent du son conditionnel, a généralement provoqué une réaction de blocage conditionné, fournissant ainsi l'expression électroencéphalographique du processus de la « généralisation sensorielle » décrit par Pavlov (cf. protocole I). Par contre, il a toujours suffi de répéter ce son sans le renforcer pour voir se développer l'inhibition de différenciation qui empêche le blocage conditionné pendant le stimulus négatif mais qui le laisse apparaître pendant le stimulus positif. Cette inhibition de différenciation se développe plus lentement que celle de l'extinction, mais elle ne demande cependant que quelques non-renforcements pour se manifester de façon évidente (cf. protocoles I et II).

L'inhibition de retard survient théoriquement lorsqu'on retarde l'application du stimulus inconditionnel de façon à accroître l'intervalle qui le sépare du stimulus conditionnel; cette inhibition se manifeste par un retard proportionnel de la réponse réflexo-conditionnée qui apparaît très peu de temps avant le moment où devrait être délivré le stimulus inconditionnel.

Dans nos expériences, le seul fait de doubler ou de tripler la durée du son conditionnel régulièrement renforcé, a toujours suffi pour réduire ou pour supprimer la réaction de blocage conditionné. Dans la plupart des cas, il nous a suffi de répéter quelquefois la combinaison sensorielle ainsi retardée pour voir le blocage conditionné disparaître pendant la plus grande partie du son et se manifester seulement quelques instants avant l'application de la lumière ou de l'ordre verbal. La comparaison de ces résultats avec ceux obtenus par Pavlov permet donc de distinguer deux phases dans les manifestations électroencéphalographiques qui accompagnent le retard: une « phase passive », sans blocage conditionné, et une « phase active », où le blocage apparaît comme une véritable réaction conditionnée au temps.

Le processus d'inhibition interne s'est donc toujours manifesté à nous, de façon *indirecte,* par la disparition de la réaction de blocage conditionné. Dans certains cas, cependant, ce processus s'est manifesté de façon *directe,* positive, par une recrudescence d'amplitude du rythme cortical. C'est-à-dire que nous avons plusieurs fois observé l'augmentation d'amplitude des rythmes corticaux, au lieu de leur blocage conditionné, pendant l'application du son non-renforcé, du son négatif ou du son prolongé. Cette recrudescence d'amplitude qui représente l'expression électroencéphalographique *positive* de l'inhibition interne occupe évidemment le même territoire que le blocage conditionné qu'elle remplace. C'est-à-dire qu'elle est localisée et que son siège varie suivant la nature du stimulus inconditionnel utilisé dans l'expérience:

a) siège occipito-parieto-temporal pour le stimulus lumineux,

b) siège rolandique pour les afférences somesthésiques,

c) siège rolandique et transitoirement occipital quand le stimulus inconditionnel est à la fois lumineux et somesthésique (dans ce cas l'inhibition se manifeste là où était le blocage conditionné).

2° *Etude électroencéphalographique de l'inhibition externe.*

Il est bien connu qu'un stimulus quelconque survenant avant le moment d'application du signal conditionnel joue un rôle perturba-

teur envers le réflexe conditionné qu'il inhibe ; c'est pour expliquer ce phénomène que I. P. Pavlov avait créé la notion d'inhibition externe.

Il nous a été très facile de démontrer l'existence de cette inhibition puisque, dans la plupart de nos expériences, un stimulus nouveau appliqué avant le signal conditionnel a suffi à contrarier son effet : soit en empêchant l'apparition du blocage conditionné, soit, au contraire, en faisant réapparaître le blocage conditionné si celui-ci avait préalablement disparu sous l'effet de l'extinction ou si le signal conditionnel était négatif.[1]

Ces manifestations indirectes de l'inhibition externe s'accompagnent évidemment de manifestations électroencéphalographiques directes, positives, qui surviennent pendant et après l'application du stimulus perturbateur.

On observe d'abord que le stimulus perturbateur provoque un blocage généralisé de tous les rythmes corticaux, c'est-à-dire qu'il se comporte comme un stimulus nouveau producteur de surprise.

On observe ensuite que ce blocage généralisé est suivi d'une recrudescence transitoire de l'amplitude des rythmes corticaux ; phénomène déjà décrit par Maiortchik et Spirine (1951), par Gastaut et Bert (1953), et par G. et J. Verdeaux et R. Frances (1955), qui ont tous rattaché ce « rebondissement » du rythme cortical à un phénomène d'inhibition produit de façon réciproque par le processus d'excitation responsable du blocage généralisé.

Il apparaît alors clairement que les manifestations électroencéphalographiques positives de l'inhibition externe sont doubles et qu'elles correspondent à deux mécanismes antagonistes d'excitation généralisée et d'inhibition généralisée. Encore faut-il reconnaître que ces deux manifestations ne sauraient représenter l'expression électroencéphalographique de toute l'inhibition externe qui se manifeste longtemps encore après que les rythmes corticaux aient récupéré leur amplitude normale.

3° *Etude électroencéphalographique de l'inhibition supra-maximale.*

A. *Manifestations électroencéphalographiques de l'inhibition supra-maximale par stimulation conditionnelle intense.*

Cette inhibition est bien connue en réflexologie conditionnelle classique où l'on sait que l'utilisation d'un stimulus conditionnel trop fort détruit la règle du parallélisme entre l'intensité du stimulus et son effet, c'est-à-dire qu'elle provoque une réponse réflexo-conditionnée plus faible que celle obtenue avec un stimulus d'intensité moyenne.

Il existe un équivalent électroencéphalographique manifeste de cette inhibition supra-maximale, puisque le seul fait d'intensifier considérablement le son conditionnel suffit à supprimer la réponse conditionnée lors de la combinaison suivante. Toutefois il ne s'agit là que d'une expression indirecte de cette inhibition supra-maximale dont l'expression électroencéphalographique positive est la même que celle de l'inhibition externe. L'application du son conditionnel trop intense ne provoque pas en effet le blocage conditionné localisé obtenu avec le son conditionnel habituel, mais il entraîne à sa place un blocage généralisé de tous les rythmes corticaux suivi du même « rebondissement » que nous avons déjà signalé à propos de l'inhibition externe.

B. *Manifestations électroencéphalographiques de l'inhibition supra-maximale par répétition.*

On sait que la répétition d'un stimulus conditionnel ou inconditionnel d'intensité faible ou moyenne entraîne une inhibition progressive de son effet. Il ne saurait être question d'identifier cette inhibition à celle de l'extinction, puisqu'elle survient sous l'effet de la répétition de stimuli inconditionnels aussi bien que conditionnels, même quand ceux-ci sont renforcés. L'inhibition supra-maximale de répétition représente le processus inhibiteur fondamental, celui qui neutralise l'effet de tout signal qui, à force d'être répété, perd progressivement sa signification. On peut donc s'étonner de voir qu'un processus d'une telle importance est le seul à n'avoir jamais été abordé du point de vue électroencéphalographique chez l'homme.

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[1] Il s'agit alors d'une inhibition externe de l'inhibition interne d'extinction ; c'est-à-dire de ce processus de *désinhibition* sur lequel Pavlov a tellement insisté.

Nous avons étudié ce phénomène chez 48 sujets.

a) Etude électroencéphalographique de la répétition de signaux *inconditionnels.*

Chez 20 sujets nous avons étudié les modifications qui accompagnent la répétition d'un stimulus initialement producteur d'une réaction de surprise. A la première stimulation nous avons toujours observé les éléments habituels de cette réaction, c'est-à-dire un blocage électroencéphalographique généralisé, quelquefois précédé d'une pointe-vertex et toujours suivi d'une variation psycho-galvanique plus ou moins importante. Lors des stimulations consécutives nous avons toujours observé l'atténuation plus ou moins rapide et progressive de ces différents éléments et notamment du blocage généralisé de l'EEG qui finit par disparaître à moins que le stimulus ne soit trop intense ou trop chargé de signification pour le sujet.[1]

b) Etude électroencéphalographique de la répétition de signaux *conditionnels renforcés.*

L'étude de 28 sujets nous a montré que la régularité du renforcement n'est pas suffisante pour perpétuer la réaction de blocage conditionné qui s'atténue et finit par disparaître après un nombre de combinaisons qui varie beaucoup d'un cas à l'autre (de 6 à 20 avec un minimum de 4 et un maximum de 47).

Qu'elle soit provoquée par la répétition de stimuli inconditionnels ou conditionnels, l'inhibition supra-maximale de répétition ne s'exprime pas seulement de façon indirecte, c'est-à-dire par la disparition progressive de la réaction de blocage, mais aussi de façon directe, positive, par l'apparition d'une manifestation électroencéphalographique nouvelle: augmentation d'amplitude de l'ensemble des rythmes corticaux, notamment du rythme alpha qui s'étend vers les régions antérieures et tend à recouvrir l'ensemble du scalp comme il le fait au tout début de l'endormissement spontané ou provoqué (cf. protocole III).

Cette recrudescence d'amplitude et d'étendue du rythme fondamental disparaît rapidement lorsqu'on interrompt la répétition du stimulus. Si, au contraire, on entretient cette répétition et surtout si on l'effectue à intervalles de temps réguliers, on peut voir survenir un phénomène nouveau encore plus caractéristique: la disparition brutale du rythme alpha et l'apparition concomitante de rythmes lents appartenant à la bande thêta. L'analogie avec les tracés caractéristiques de l'endormissement est cette fois d'autant moins discutable qu'à ce moment de l'expérience le sujet est calme, détendu et qu'il présente peu de mouvements spontanés.

A cette phase de sommeil électrique léger, le stimulus conditionnel est encore capable de provoquer une réaction d'éveil caractérisée par le retour soudain du rythme alpha et la disparition concomitante des ondes thêta (protocole III). Ultérieurement, quand les tracés sont encore plus ralentis (apparition d'ondes delta), le stimulus conditionnel est sans effet et la réaction électroencéphalographique d'éveil ne survient plus que pendant l'application du stimulus inconditionnel (c'est-à-dire de la lumière qui provoque toujours la contraction du poing, protocole III).

On peut considérer que la réaction d'éveil provoquée par le stimulus inconditionnel alors que le stimulus conditionnel est sans effet, correspond en quelque sorte à la *phase normale* de l'inhibition décrite par Pavlov, pendant laquelle un stimulus fort provoque une réaction plus importante qu'un stimulus faible. La continuation de l'expérience permet quelquefois d'observer la *phase d'égalisation* de Pavlov, pendant laquelle le stimulus le plus faible (son) retrouve son efficacité et provoque à nouveau la réaction d'éveil au même titre que le stimulus le plus fort (lumière). Dans un cas nous avons pu noter une phase électroencéphalographique *paradoxale,* pendant laquelle le son provoquait une brève réaction d'éveil alors que la lumière était sans effet. Peu après cette phase nous avons même observé une réaction électroencéphalographique conditionnée au temps qui nous a semblé confirmer l'efficacité plus grande de facteurs habituellement inhibés dans les conditions de veille. Alors que la lumière et le son étaient devenus entièrement inefficaces, nous avons pu observer une réaction d'éveil électroencéphalographique très nette survenant sponta-

[1] S. Dongier, Y. Gastaut et M. Dongier, qui ont particulièrement étudié ce problème (1955) ont démontré que la rapidité de cette inhibition dépend en grande partie de la constitution du sujet.

nément une ou deux secondes avant l'application de la combinaison suivante, témoignant ainsi d'un véritable conditionnement à l'intervalle de temps qui séparait les combinaisons entre elles (30 sec. dans le cas étudié).

On peut donc affirmer que l'inhibition supra-maximale de répétition s'exprime positivement de façon diffuse sur l'EEG et qu'elle revêt l'aspect des différentes étapes de l'endormissement ou du sommeil léger. Il s'agit d'ailleurs d'un sommeil électrique et non clinique, ou du moins d'un sommeil clinique très superficiel, car le sujet continue de se conformer aux consignes préalables et ne se souvient pas d'avoir dormi.

4° *Interprétation des réactions électroencéphalographiques conditionnées, à la lumière des théories Pavloviennes sur le processus de l'inhibition centrale.*

Nous voudrions maintenant voir dans quelle mesure les manifestations électroencéphalographiques que nous avons observées confirment ou même développent les hypothèses émises par Pavlov sur la nature, le siège et la mobilité du processus d'inhibition centrale.

A. Notre étude confirme doublement l'existence d'un processus d'inhibition centrale: de façon négative, en montrant les effets indirects de cette inhibition (disparition des réactions de blocage préalablement conditionnées), de façon positive en montrant que le processus inhibiteur possède une expression électroencéphalographique directe et uniforme (augmentation d'amplitude et, éventuellement, diminution de fréquence du rythme cortical).

Uniformité qui s'accorde d'ailleurs avec l'opinion de Pavlov et de Vvedenski suivant qui l'inhibition centrale reconnaît une nature unique sous quelque forme qu'elle se présente.[1]

Cet aspect électroencéphalographique positif de l'inhibition centrale est très important dans la mesure où il empêche de se représenter cette inhibition comme une simple diminution du processus d'excitation. Il confirme au contraire l'hypothèse d'une inhibition active soutenue par Pavlov et oblige de se la représenter, suivant l'expression imagée d'Oukhtomski, comme un véritable « repos actif », c'est-à-dire comme un processus positif engendré par des afférences qui, en d'autres circonstances, auraient provoqué de l'excitation.

B. L'étude chronologique des manifestations électroencéphalographiques de l'inhibition centrale fait ressortir la rapidité de son installation, de son évolution et de sa disparition. On peut dire qu'une réaction électroencéphalique conditionnée s'inhibe aussi vite qu'elle s'est acquise et se restaure aussi vite qu'elle s'est inhibée. On pourrait donc se demander si la mobilité des processus d'inhibition ne jouerait pas un rôle dans l'adaptabilité, la plasticité et la versatilité du comportement humain.

C. L'étude topographique des manifestations électroencéphalographiques de l'inhibition centrale fait ressortir une différence fondamentale entre, d'une part l'inhibition externe et les deux variétés d'inhibition supramaximale, qui s'expriment par une hypersynchronie corticale *généralisée*, et d'autre part les trois variétés d'inhibition interne qui s'expriment au contraire par une hypersynchronisation *localisée*.

Il est intéressant de remarquer que nos trois variétés d'inhibition généralisée répondent aux trois variétés d'inhibition inconditionnelle de Pavlov, tandis que nos trois variétés d'inhibition localisée répondent aux trois variétés d'inhibition conditionnelle du même auteur.[2]

Si l'on associe maintenant les données topographiques et chronologiques recueillies au cours de notre étude sur les états d'excitation et d'inhibition centrale. on arrive à distinguer ces états en 4 grandes variétés:

1 En ce qui concerne l'uniformité de l'expression électroencéphalographique positive de l'inhibition centrale, elle n'est pas évidente si l'on commet l'erreur de prendre comme manifestation exclusive ou même principale de l'inhibition externe le blocage généralisé qui accompagne l'application du stimulus perturbateur (Popov 1954, 1955).

2 Ce fait est d'autant plus intéressant que Skipine a pu démontrer, sans le secours de l'EEG, que l'inhibition interne est un phénomène local développé au niveau de l'analyseur inconditionnel, tandis que l'inhibition externe est un phénomène général qui intéresse l'ensemble du cortex.

Un processus d'*excitation généralisée, non conditionnée,* qui survient chaque fois que le cerveau reçoit un signal qualitativement ou quantitativement nouveau; processus responsable des réactions inconditionnelles de surprise et d'attention avec toutes leurs composantes, notamment la désynchronisation généralisée.

Un processus d'*excitation localisée, conditionnée,* qui survient chaque fois que le cerveau reçoit un signal connu, ayant acquis une signification particulière du fait de sa combinaison préalable avec d'autres signaux ontologiquement ou historiquement significatifs; processus responsable des réactions conditionnées qui président à l'adaptation et à l'apprentissage.

Un processus d'*inhibition localisée, conditionnée,* qui survient chaque fois qu'un signal connu perd sa signification conditionnelle; processus qui joue également un rôle capital dans l'adaptation puisqu'il est responsable de la suppression des réactions conditionnées devenues inutiles ou nuisibles.

Un processus d'*inhibition généralisée, non conditionnée,* qui survient:

a) chaque fois que le cerveau a reçu un signal nouveau générateur d'une réaction de surprise ou d'attention. Il s'agit alors d'une inhibition induite de façon réciproque et destinée à rétablir un équilibre en neutralisant le processus d'excitation généralisée qui lui a donné naissance;

b) chaque fois que l'on répète un signal nouveau ou connu, générateur de réaction de surprise inconditionnée ou de réaction d'adaptation conditionnée. Il s'agit alors d'une accumulation de l'inhibition précédente, destinée à protéger le sujet contre cette répétition inutile ou nuisible, fusse au prix de sommeil.

Quelle que soit la valeur de la classification que nous proposons, il nous reste encore à la soumettre à la critique neuro-physiologique en cherchant les moyens d'expliquer sur des bases anatomiques et fonctionnelles les réactions électroencéphalographiques diffuses et localisées qui ont dirigé notre raisonnement.

V — INTERPRÉTATION NEURO-PHYSIOLOGIQUE DES RÉACTIONS ÉLECTROENCÉPHALOGRAPHIQUES CONDITIONNÉES

La connaissance récente de la physiologie des structures régulatrices sous-corticales, associée à celle des manifestations électroencéphalographiques du conditionnement que nous venons de rapporter, permettent de suggérer quelques hypothèses neuro-physiologiques que nous voudrions développer en trois étapes successives:

1° *Interprétation neuro-physiologique des phénomènes électroencéphalographiques qui précèdent le conditionnement.*

Le point de départ de toute réaction conditionnée, comme celui de toute réaction d'ajustement de l'organisme, est évidemment le *signal,* dont la valeur d'information varie considérablement suivant qu'il est fourni pour la première fois ou qu'il a déjà été répété.

A. *Lorsqu'il est appliqué pour la première fois,* le signal provoque, suivant ses caractères qualitatifs et surtout quantitatifs, une réaction de surprise ou une réaction d'attention. Réactions inconditionnelles d'alerte qui sont d'ailleurs très voisines et possèdent une expression végétative commune quoique plus accusée dans l'effet de surprise: suspension de la respiration, accélération cardiaque et abaissement de la résistance cutanée. Ces réactions présentent également une expression électroencéphalographique commune puisque toutes deux s'accompagnent d'un blocage généralisé des rythmes corticaux quelquefois précédé d'une pointe sur le vertex dans l'effet de surprise. Seules les manifestations somatiques[1] diffèrent, elles sont simples dans l'effet de surprise, revêtant l'aspect bien connu du sursaut, tandis qu'elles sont très complexes dans la réaction d'attention où elles réalisent l'équivalent du phénomène décrit par Pavlov chez le chien sous le nom de « réflexe d'orientation »: interruption soudaine de l'acte en cours, augmentation du tonus avec fixation de la posture, discret élargissement des fentes palpébrales avec déplacement des

[1] A dire vrai les manifestations psychiques diffèrent également. Elles sont très simples dans les réactions de surprise, plus complexes dans les réactions d'attention.

globes oculaires (quelquefois même de la tête) vers le côté d'où provient le signal.

Bien que le mécanisme de ces deux réactions n'ait pas encore fait l'objet de recherches neuro-physiologiques systématiques, il semble que l'on puisse élaborer des hypothèses précises à leur sujet.

Il est bien établi, en effet, que tout stimulus provoque une volée corticipète qui circule dans les voies sensitivo-sensorielles aboutissant à l'analyseur cortical, pour y provoquer d'une part le potentiel évoqué spécifique et d'autre part les phénomènes psycho-physiologiques impliqués dans la perception. Mais il est aussi bien établi que la même volée aboutit à la substance réticulée du tronc cérébral grâce aux collatérales réticulopètes des fibres lemniscales mises en évidence par Starzl et Col. Ce sont ces afférences réticulopètes que nous rendons responsables des différentes manifestations des réactions d'alerte, supposant que leur sommation spatiale et temporelle sur les neurones réticulés provoque un état d'excitation intense qui se propagerait le long des voies réticulo-bulbo-spinales activatrices et inhibitrices pour provoquer :

l'activation motrice périphérique responsable du sursaut ou de l'accroissement tonique avec fixation de l'attitude ;

l'activation des centres végétatifs préganglionnaires responsables des modifications respiratoires, cardiaques et sécrétoires ;

l'inhibition des relais périphériques des systèmes sensoriels [1] permettant la polarisation de l'attention sur le signal en cause.

Cette excitation réticulée se propagerait également de façon centripète le long des voies ascendantes diffuses pour provoquer :

La désynchronisation des rythmes corticaux responsables de la réaction de blocage ;

l'ensemble des phénomènes moteurs, principalement déviationnels, responsables du réflexe d'orientation.

Le mécanisme réticulé que nous avons proposé a encore l'avantage d'expliquer les manifestations électroencéphalographiques qui succèdent immédiatement aux réactions de surprise et d'attention et dont la plus spectaculaire est une recrudescence d'amplitude du rythme fondamental préalablement désynchronisé. Les expériences cruciales de Lindsley, Bowden et Magoun (1949) nous ont appris en effet que la destruction de la formation réticulée du tronc cérébral provoque une hypersynchronisation corticale généralisée et nous savons par les travaux de A. Roger, Rossi et Zirondoli (1954), que la simple désafférentiation réticulée aboutit aux mêmes résultats. Il est donc logique de supposer que l'excitation réticulée responsable des réactions d'alerte et de leur désynchronisation doit laisser place à un processus d'inhibition locale responsable du renforcement consécutif des rythmes corticaux.

B. *Lorsqu'il est répété à intervalles de temps suffisamment rapprochés* le signal perd progressivement sa signification d'alarme et ne provoque plus les réactions de surprise ni d'attention. Nous sommes donc en présence d'un phénomène d'adaptation que l'on désigne quelquefois sous le nom d'habituation et qui répond en fait à l'inhibition de répétition que nous avons longuement étudiée au chapitre précédent.

Sous l'effet de cette adaptation le signal répété n'entraîne plus de manifestations végétatives ni somatiques et ne provoque plus que des modifications électroencéphalographiques dont l'importance et la nature varient en fonction des répétitions :

a) après quelques répétitions, le signal ne provoque plus de blocage généralisé, mais seulement une désynchronisation localisée à la région correspondant à l'analyseur en cause (c'est-à-dire à la région rolandique pour les stimuli somesthésiques et à la région temporo-parieto-occipitale pour les stimuli visuels et auditifs) ;

b) après un plus grand nombre de répétitions le blocage localisé disparaît à son tour ;

c) si on continue les répétitions surviennent enfin les phénomènes de synchronisation lente généralisée évocateurs du sommeil.

Pour l'interprétation neuro-physiologique de ces phénomènes il faut rappeler tout d'abord que nous avons déjà rapporté le blocage généralisé, qui accompagne la réaction d'a-

[1] Phénomènes d'inhibition sensorielle périphérique et thalamique démontrés par Hagbarth et Kerr ; Hernandez Peon et Col. ; King, Naquet et Magoun.

lerte, à une activation de la formation réticulée du tronc cérébral dont on sait que sa stimulation électrique provoque une désynchronisation généralisée du cortex (Moruzzi et Magoun 1949). Ceci nous conduit évidemment à rapporter le blocage localisé qui lui succède au début de l'habituation à une activation partielle de la substance réticulée du thalamus dont les travaux de Jasper et Col. ont montré qu'elle s'accompagne d'une désynchronisation localisée du territoire cortical correspondant. Hypothèse qui nous paraît d'autant plus valable que Jasper, Naquet et King (1955) sont parvenus à distinguer dans le système intra-laminaire du thalamus une région médio-ventrale et une région latéro-dorsale projetant respectivement sur les parties antérieures et postérieures du cortex que nous sommes justement parvenus à désynchroniser en utilisant des stimuli sensoriels (somesthésiques ou visuels et auditifs).[1]

Autrement dit, nous en arrivons à impliquer les deux étages mésencéphalique et diencéphalique (thalamique) de la formation réticulée dans le processus d'adaptation qui fait passer de l'état d'alerte à celui de vigilance; point de vue qui diffère à peine de celui présenté par Jasper et Ajmone Marsan lorsqu'ils écrivaient en 1952: « The regulating effects appear to arise from the reticular formation of diencephalon and mid-brain. From the thalamic portion of this system the regulatory action can be limited to only one specific system, which suggests a mechanism for the central control of attentive processes. This may be a differentiation of the generalized arousal mechanism which is mediated through lower portions of the reticular formation. »

Si on implique, comme nous le proposons, les deux « systèmes d'éveil » de Moruzzi-Magoun d'une part, et de Jasper d'autre part, dans le processus d'habituation, on arrive à la conclusion que tout signal nouveau, cause d'une réaction d'alerte, agit sur la partie la plus basse, la moins différenciée, de la formation réticulée, tandis que le signal répété, privé de sa valeur d'alarme, agit sur la partie la plus haute, la plus différenciée, de cette même formation. Pour expliquer cette action topographiquement différente d'un même signal en cours d'adaptation, le plus simple nous semble d'admettre que les fibres spécifiques dans lesquelles il circule, envoient des collatérales aux deux niveaux correspondants de la formation réticulée, mais que le niveau le plus bas est plus rapidement inhibé au cours du processus d'adaptation.

Suivant cette hypothèse, tout signal nouveau provoque la désynchronisation généralisée parce qu'il agit, dès son entrée dans le tronc cérébral, sur la formation réticulée la plus basse et sur le système de projection cortical diffus. Quant aux signaux subséquents, l'inhibition progressive de la formation réticulée du tronc cérébral les empêche d'agir sur ce même système diffus, et de désynchroniser par son intermédiaire l'ensemble du cortex, tandis qu'elle les laisse parvenir jusqu'au système thalamo-cortical responsable de la désynchronisation localisée. Bien plus, il est probable que l'inhibition du système diffus mésencéphalique facilite la mise en jeu du système localisé thalamo-cortical, ainsi qu'il ressort des expériences de Jasper, Naquet et King (1955) et de King (1956), suivant qui la destruction ou le blocage anesthésique de la réticulée du tronc cérébral favorise l'action corticale localisée du système de projection non spécifique du thalamus. Cette notion d'antagonisme entre le système d'éveil généralisé de Moruzzi et Magoun et celui partiel de Jasper, est d'une importance particulière dans la mesure où elle permet de considérer la désynchronisation localisée du cortex qui

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[1] Nous avons déjà signalé, en effet, que nous ne sommes parvenus à désynchroniser que la région rolandique en utilisant des stimuli somesthésiques ou la région occipito-parieto-temporale en employant des stimuli visuels ou auditifs (nous ne sommes pas arrivés notamment à bloquer électivement le rythme occipital avec des stimuli visuels ni le rythme temporal avec des stimuli auditifs, mais seulement le rythme occipito-temporal et même pariétal avec ces deux sortes de stimuli). Pareilles constatations nous ont fait supposer que les signaux physiologiques n'agissent sur le cortex que par l'intermédiaire d'un des deux systèmes mis en évidence par Jasper et ses collaborateurs, cette convergence de signaux différents sur des structures thalamo-corticales communes ayant pour effet de leur assurer une communauté d'action. C'est ainsi que nous sommes arrivés à la conclusion que le blocage cortical rolandique doit correspondre à l'ensemble des signaux extéroceptifs, proprioceptifs et interoceptifs renseignant l'individu sur l'état de son corps, tandis que le blocage localisé aux régions occipito-pariéto-temporales doit correspondre aux signaux visuels ou auditifs qui le renseignent sur le milieu environnant.

survient au cours de l'habituation, comme une activité positive, résultant de la facilitation d'un système bien défini, et non pas comme un simple vestige du blocage cortical généralisé de l'alerte.

Pour en revenir à l'inhibition réticulée, nous admettons qu'elle continue de s'accumuler lors de la répétition du signal, envahissant progressivement le système de projection thalamo-cortical et entraînant la disparition de la réaction de blocage localisée. Ainsi se trouve réalisé un stade d'indifférence électroencéphalographique pendant lequel le stimulus répété n'entraîne aucune modification des rythmes corticaux. Ce stade d'« adaptation » complète est cependant transitoire, car l'accumulation progressive de l'inhibition réticulée sous l'effet de la répétition, atteint rapidement un niveau suffisant pour libérer la synchronisation généralisée caractéristique du sommeil électrique léger. A ce stade le phénomène de l'adaptation est dépassé, laissant place à un processus de « protection » pouvant aboutir au sommeil confirmé.

2° *Interprétation neuro-physiologique des phénomènes électroencéphalographiques qui accompagnent le conditionnement.*

Nous avons vu que le fait d'être combiné plusieurs fois de suite avec le signal absolu (non entièrement adapté puisqu'il désynchronise toujours le territoire correspondant à son analyseur cortical) confère au signal indifférent (entièrement adapté puisqu'il ne modifie plus l'EEG) la propriété de bloquer à nouveau les rythmes corticaux.

Ce blocage nouveau, dit conditionnel, présente toutefois une grande particularité dans la mesure où il n'intéresse pas le territoire correspondant de l'analyseur cortical du signal en cause, mais celui du signal absolu auquel il est combiné. Il faut donc admettre que le signal indifférent ne chemine plus dans les mêmes voies thalamo-corticales à partir du moment où il est devenu conditionnel et qu'il emprunte depuis lors celles qui étaient réservées à la transmission du signal absolu, inconditionnel.

Autrement dit, nous admettons un aiguillage nouveau du signal conditionnel dans le thalamus qui implique la création de « liaisons temporaires » que notre raisonnement nous permet de situer dans la formation réticulée thalamique.[1]

L'hypothèse de la fermeture sous-corticale des arcs réflexes conditionnels, à laquelle nous aboutissons sur des bases électroencéphalographiques, s'accorde d'ailleurs avec les expériences de facilitation et d'inhibition des réflexes conditionnés par stimulation réticulée qui ont permis à Lissak d'écrire en 1955 : « Les expériences d'activation des systèmes de projection diffuse et l'influence de la stimulation hypothalamique sur les processus conditionnels nous permettent de supposer que la fermeture des réflexes conditionnés doit se faire d'abord quelque part dans les régions sous-corticales. » Il n'est pas jusqu'à Pavlov qui n'ait envisagé cette hypothèse, tout en lui préférant celle de la fermeture corticale, puisqu'il écrivait : « Où se produit exactement la fermeture ? Exclusivement dans l'écorce des hémisphères, ou bien avec la participation des étages sous-jacents du cerveau ? On peut admettre les deux possibilités. »

Le rôle essentiel accordé par Pavlov au mécanisme cortical du conditionnement n'est d'ailleurs pas minimisé par notre hypothèse d'une liaison sous-corticale. Nous avons vu, en effet, que la fermeture thalamique de l'arc réflexe conditionnel s'accompagne toujours d'une activation des projections thalamo-corticales non spécifiques correspondantes, avec excitation élective d'un vaste territoire cortical comportant l'analyseur du stimulus inconditionnel.[2] Il nous semble évident que cette activation corticale secondaire doit

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1 Un tel aiguillage a déjà été proposé par l'un de nous qui écrivait : « Le moment où les influx bifurquent dans le thalamus vers une autre région corticale devrait correspondre à l'ouverture de portes synaptiques antérieurement fermées... L'hypothèse d'une position nouvelle acquise dans une sorte de système de commutation diencéphalique me paraît heureuse » (Gastaut 1953).

2 Il est intéressant de remarquer que dans son hypothèse corticale Pavlov lui-même faisait jouer un rôle prépondérant au foyer d'excitation inconditionnel. C'est ainsi que parmi trois possibilités de liaison temporaire corticale, il en admettait une où « le signal conditionnel provoque directement des modifications dans les points de l'écorce liés au réflexe inconditionnel, après quoi l'excitation se transmet vers la couche sous-corticale et vers la périphérie ». Récemment encore Livanov soutenait le même point de vue en écrivant : « L'excitant conditionnel s'adresse de préférence directement au centre cortical de l'excitant inconditionnel et de là à la périphérie. »

jouer un très grand rôle dans l'élaboration de l'activité conditionnée et si nous devions abandonner momentanément notre point de vue exclusivement électroencéphalographique pour appliquer notre théorie aux phénomènes moteurs du conditionnement, nous aboutirions à la conception suivante:

a) la fermeture sous-corticale de l'arc conditionnel se traduirait à la périphérie par une activité réflexe globale, non adaptée et peu sujette à la différenciation, qui persiste après décortication (par exemple: le mouvement de retrait global d'un animal fixé, qui survient lorsqu'un bruit annonce une décharge électrique douloureuse et inévitable);

b) l'activation correspondante du territoire cortical « inconditionnel » serait responsable de l'adaptation et de la différenciation fine du phénomène réflexo-conditionné grossier, d'origine sous-corticale. (Par exemple: les divers comportements d'évitement que peut utiliser un animal libre lorsqu'il entend des sons différents annonciateurs de l'électrisation de telle ou telle partie du plancher de sa cage).

3° *Interprétation neuro-physiologique des phénomènes électroencéphalographiques qui suivent le conditionnement.*

Nous savons qu'une réaction électroencéphalographique conditionnée peut toujours être abolie de façon plus ou moins rapide et plus ou moins durable par des processus inhibiteurs plus ou moins spécifiques.

A. C'est ainsi qu'il existe une inhibition non-spécifique susceptible de supprimer momentanément l'effet de tout signal conditionnel aussi bien qu'inconditionnel; inhibition que Pavlov qualifie d'« inconditionnelle », et qui comprend l'ensemble des faits que nous avons étudiés sous le nom d'inhibition externe et d'inhibition supra-maximale. Nous ne ferons que rappeler son mécanisme qui a déjà été envisagé dans le chapitre consacré aux manifestations électroencéphalographiques accompagnant l'application d'un signal nouveau ou répété; mécanisme double qui comprend:

a) une inhibition périphérique, bloquant les premiers relais sensoriels, résultant elle-même d'un foyer d'excitation développé dans la réticulée sous l'effet des afférences déclenchées par un signal producteur d'une réaction de surprise ou d'attention (Jouvet et Hernández Peón 1955);

b) une inhibition centrale, développée de façon réciproque dans la réticulée sous l'effet du foyer d'excitation précédemment envisagé; inhibition susceptible de s'accumuler lorsqu'on répète le signal et de se généraliser à l'ensemble du cerveau par le moyen des projections ascendantes diffuses.

Ces deux mécanismes jouent un rôle dans le développement de toutes les variétés d'inhibition inconditionnelle, mais il est certain que le premier concerne plus particulièrement l'inhibition externe et l'inhibition supra-maximale qui succède à l'application d'un signal conditionnel trop intense, tandis que le deuxième concerne exclusivement l'inhibition supra-maximale de répétition.

B. Il existe d'autre part des processus inhibiteurs qui agissent électivement sur un signal conditionnel particulier. Ces inhibitions qualifiées de « conditionnelles » par Pavlov répondent aux phénomènes d'extinction, de différenciation et de retard.

Nous savons que cette inhibition conditionnelle s'oppose à l'inhibition inconditionnelle par le caractère focalisé et non pas généralisé des réactions électroencéphalographiques qui l'accompagnent. Le signal éteint, différencié ou retardé, provoque en effet une hypersynchronisation localisée au territoire préalablement désynchronisé par le stimulus conditionnel; inversion d'effet qui ne nous paraît explicable qu'en supposant le développement d'une inhibition localisée dans le système thalamo-cortical précédemment activé par le stimulus conditionnel.

Cette hypothèse qui prend la désynchronisation et l'hypersynchronisation d'un territoire cortical comme signe de l'excitation ou de la dépression fonctionnelle du secteur thalamo-cortical correspondant nous semble objectivée par les deux expériences suivantes:

a) la synchronisation lente du cortex visuel obtenue par stimulation itérative du système non spécifique thalamique correspondant est électivement bloquée par la stimulation visuelle (Jasper, Naquet et King 1955).

b) la suppression des afférences visuelles provoque au contraire la synchronisation lente du cortex visuel (Claes 1939).

Ainsi la distinction des deux étages mésencéphalique et diencéphalique de la formation réticulée, qui a déjà fourni l'explication des phénomènes d'excitation centrale généralisée et localisée, sert également à expliquer les phénomènes généralisés et localisés de l'inhibition.[1]

SUMMARY

I and II. Methods and results.

The authors have undertaken an EEG study of conditioning in man by means of a large number of leads permitting simultaneous exploration of several cortical regions and various somatic activities (using the electromyogram, electrocardiogram, pneumogram and electrodermogram). In some cases they used the automatic frequency analyser working simultaneously on eight cortical leads.

Sixty subjects with an occipito-parieto-temporal alpha rhythm or a rolandic rhythm "en arceau", or both, were subjected to "indifferent"[2] (ineffective) and "absolute"[3] (effective) stimuli chosen and combined so as to condition the two rhythms either independently or concomittently.

Auditory stimuli were combined with visual stimuli either steady illumination or flicker, in order to condition the alpha rhythm alone.

Auditory stimuli were combined with passive displacement of the hand or the command "clench the fist" in order to condition the rolandic rhythm alone.

The combinations of sound + light + simultaneous displacement of the hand, or of sound + light + clenching of the fist during illumination following pre-given instruction were used in order to condition both rhythms at once.

The results in these 60 subjects are classified and in 4 cases they are given in detail. Each of these cases illustrates the chief characteristics of conditioning of the occipital and rolandic rhythms.

III and IV. EEG study of the processes of central excitation and inhibition during conditioning.

The process of central excitation is made manifest during conditioning of the electrical activity of the cortex by a "blocking" response, the site of which depends exclusively on the nature of the "absolute" stimulus and not of the "indifferent" stimulus. Thus a sound previously "indifferent" blocks the controlateral rolandic rhythm when it has been combined with a somaesthetic absolute stimulus, and it blocks the bilateral occipito-parieto-temporal alpha rhythms when it has been combined with a visual absolute stimulus either steady illumination or flicker. When an indifferent sound is combined with a multiple (both visual and somaesthetic) absolute stimulus, there follows one of two topographically different EEG conditioned responses: either the bilateral alpha rhythm is blocked simultaneously with the controlateral rolandic rhythm or the controlateral rolandic rhythm alone is blocked. In the first case, however, the blocking of the alpha rhythm fades out and rapidly disappears, leaving only the persistent blocking of the contralateral rhythm « en arceau ». This latter therefore represents the essential element of the conditioned response.

When there is a motor component of the conditioned reflex (premature clenching of the fist on hearing the sound), it is always preceeded by the conditioned response of rolandic blocking. This response of contralateral rolandic blocking therefore represents a genuine cortical precursor of the peripheral action, and one may consider it as putting into play or "setting" the cortical region where the motor act will later be elaborated.

The process of central inhibition is first made manifest by the disappearance of previously conditioned "blocking" responses. However, it is also expressed in a positive way

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[1] Depuis la rédaction de cet article, les Auteurs ont eu connaissance des travaux de Grastyan, Lissak et Kekesi (*Acta Physiol. Acad. Scient. Hung.*, **1956**, *19*: 133-151) qui confirment le rôle joué par la formation réticulée dans l'élaboration des réflexes conditionnés, et des travaux de Morrell et Jasper (*EEG. Clin. Neurophysiol.*, **1956**, *8*: 201-215) qui impliquent les deux étages de la formation réticulée dans l'établissement du conditionnement électrocortical.

[2] Throughout this paper the term "indifferent" is used to describe a stimulus which previously modified the EEG mildly but which after some repetitions has lost his effect. It is thus a specific type of stimulus which is ineffective.

[3] The term "absolute" is here used to describe an unconditioned stimulus which modifies the EEG in a clear-cut specific manner. It is thus effective.

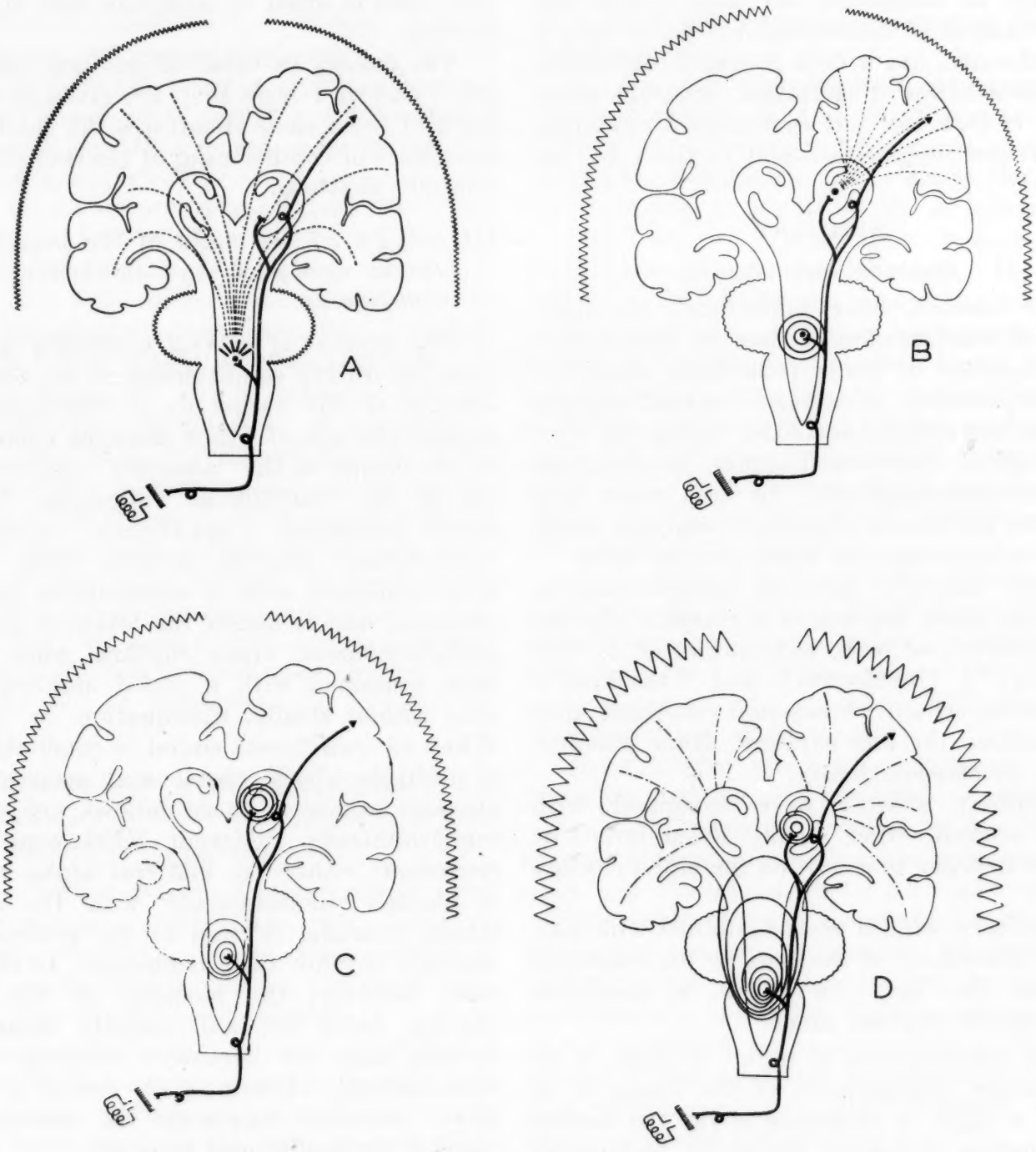

Fig. 6

Diagramatic interpretation of the EEG phenomena which accompany habituation

A. The first signal activates the reticular formation of the mesencephalon. It provokes generalised desynchronisation which constitutes the EEG expression of the surprise (startle) response.

B. After a few repeated signals, inhibition develops in the mesencephalic reticular formation and suppresses the generalised desynchronisation. It unmasks the activity of the thalamic reticular system which then provokes localised desynchronisation characteristic of the attention response.

C. After a few more repetitions, inhibition which develops in the thalamic reticular formation suppresses the localised desynchronisation. The stimulus which thus no longer modifies the EEG is termed ''indifferent'' (ineffective).

D. If signal stimuli are continued, the accumulation of reticular inhibition liberates the system responsible for spindles and provokes generalised slow synchronisation of cortical rhythms (sleep).

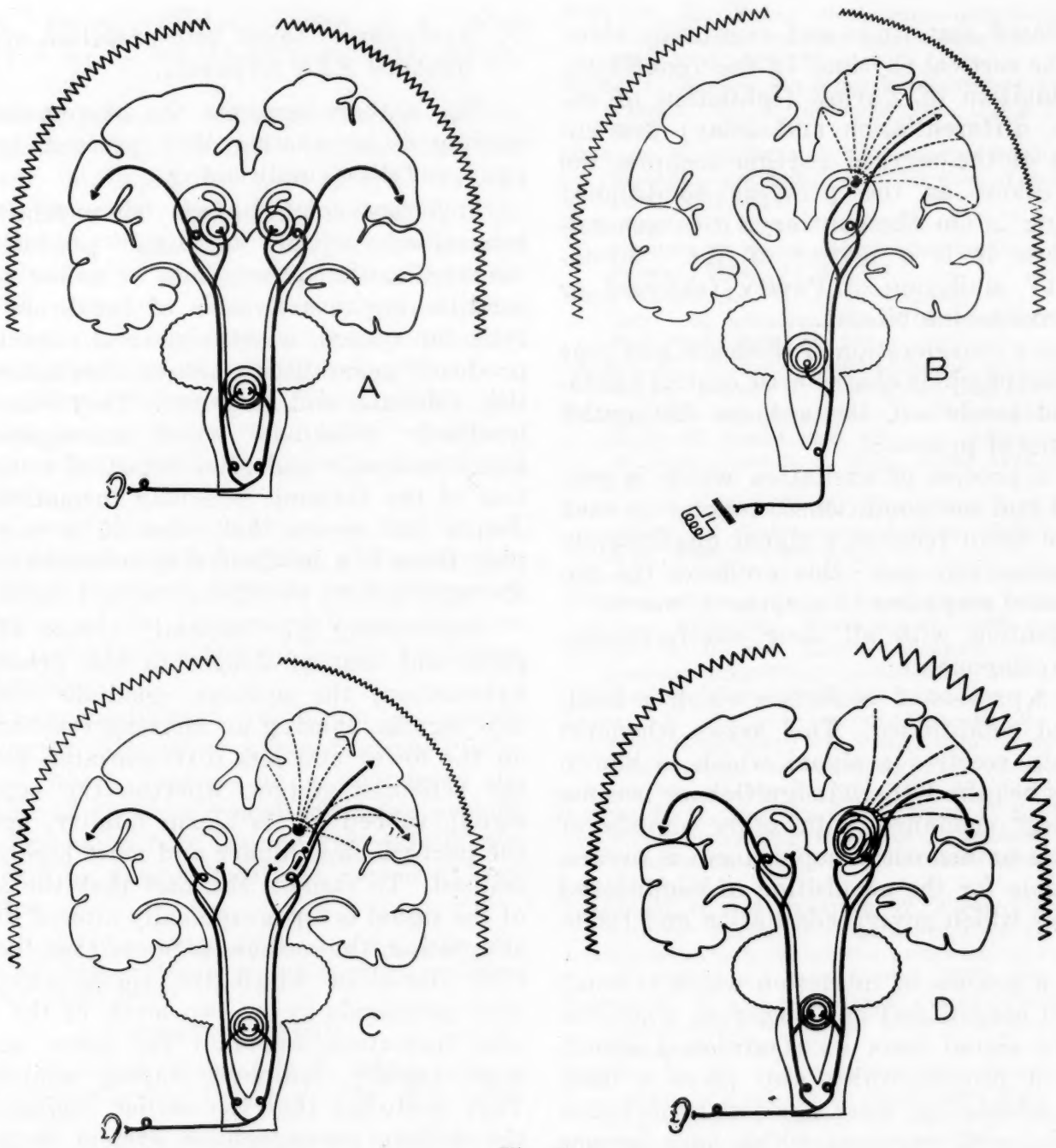

Fig. 7

Diagramatic interpretation of the EEG phenoma which accompany conditioning

A. The ''indifferent'' or ineffective stimulus (a weak sound) does not modify the EEG for it has been sufficiently repeated to lose all effects of stimulation on the reticular formation of mesencephalon and thalamus. (Reciprocal inhibition has developed around the extremities of reticulopetal collaterals: concentric circles.)

B. The ''absolute'' or effective stimulus (a somaesthetic stimulus of moderate strength) has here been repeated often enough to lose all stimulant effect on the mesencephalic reticular system, but was chosen as one of sufficient strength to continue acting on the thalamic reticularis. This results in activation of the appropriate but non-specific thalamo-cortical system (dotted lines) and in localised desynchronisation of the EEG around the somaesthetic analysing areas.

C. After the application of a certain number of combined ''indifferent'' (ineffective) and ''absolute'' (effective) stimuli, sound provokes the same EEG result as somaesthetic stimulation. One has therefore to postulate the development of a ''temporary link'' permitting thalamic collaterals borrowed by the sound signal to act on the neurones previously only activated by the collaterals of the somaesthetic signal.

D. The non-reinforcement of the conditioned stimulus (sound) creates a focus of thalamic inhibition which is responsible for the EEG expression of extinction, that is to say an electroencephalographic ''re-inforcement'' (synchronisation) by the sound.

No attention should be paid to the arrows in thick lines, which represent the specific afferents to the cortex, whose EEG expression (evoked potential) cannot be recorded from the scalp in man.

by increased amplitude and eventually slowing of the cortical rhythm. In the ''conditioned'' inhibition of Pavlov (inhibition of extinction, differentiation and delay) this enhancing of the cortical rhythm occupies the same regions as the previous conditioned ''blocking''. On the contrary, it is generalised when it is a matter of the ''unconditioned'' inhibition of Pavlov (external or supramaximal inhibition).

From a consideration of these site and time relationships which characterise central excitation and inhibition, the authors distinguish four types of process:

(1) a process of excitation which is generalized and not conditioned, coming on each time the brain receives a signal qualitatively or quantitatively new; this produces the unconditioned responses of surprise (''startle'') and attention with all their electro-psychosomatic components;

(2) a process of excitation which is localised and conditioned. This arises whenever the brain receives a signal which is known and has acquired special significance because previously combined with other signals of ontogenic or historical importance; a process responsible for the acquisition of conditioned responses which govern adaptation and learning;

(3) a process of inhibition which is localised and conditioned and comes on whenever a known signal loses its conditioned significance; a process which also plays a basic part in adaptation, since it causes suppression of conditioned responses which have become useless or harmful;

(4) a process of inhibition which is generalized and not conditioned, and appears in two different circumstances:

(*a*) whenever the brain has received a new signal producing a response of surprise or attention. It is then a matter of reciprocal inhibition, destined to restore equilibrium by neutralizing the process of generalised excitation which gave it birth;

(*b*) whenever a new or known signal is repeated. It is then a matter of accumulation of the previous inhibition, destined to protect the subject against this useless and harmful repetition, althought it may be at the price of sleep.

V. *Neurophysiological interpretation of conditioned EEG responses.*

The authors separate the phenomena according as to whether they preceed, accompany, or follow conditioning.

1. *Before conditioning.* They relate the generalised cortical ''blocking'' produced by the application of any new stimulus before conditioning to activation of the brain stem reticular system, whose electrical stimulation produces generalised cortical desynchronisation (Moruzzi and Magoun). They relate the localised ''blocking'' which accompanies a stimulus closely and often repeated to activation of the thalamic reticular formation, for Jasper has shown that when it is put into play there is a localised desynchronisation of the appropriate overlying cortical areas.

Implicating the ''arousal'' system of Magoun and that of Jasper in the process of habituation, the authors conclude that all new signals, causing an alerting reaction, act on the lower and less differentiated part of the reticular system, whereas the repeated signal, robbed of its alarm quality, acts on the part which is higher and more highly specialised. To explain the fact that the action of the signal is topographically altered during adaptation, the authors suppose that the specific fibres in which the signal circulates send collaterals to the two levels of the reticular formation, but that the lower part is more rapidly inhibited during adaptation. They postulate that the earlier inhibition of the diffuse mesencephalic system facilitates ''setting'' (putting into play) the localised thalamo-cortical system, according to the principle of functional antagonism of these two systems.

2. *During conditioning.* A signal, which had previously become ''indifferent'' (ineffective) through habituation, when combined during conditioning with an ''absolute'' (effective) signal, produces ''blocking'' of that region in which the ''absolute'' signal is normally analysed. It follows that the ''indifferent'' signal, from the moment that it becomes conditioned, no longer travels along the same thalamo-cortical pathways, but thenceforth borrows those which had been reserved for the transmission of the ''ab-

solute'' signal. (Establishment of a ''temporary link'' in the thalamic reticular formation.)

This hypothesis, whilst admitting that the ''temporary link'' is infra-cortical, does not however minimise the part played by the cortex, since the thalamic ''closure'' of the conditioned reflex-arc is always accompanied by activation of the corresponding thalamo-cortical segment. This secondary cortical activation probably plays an important part in the elaboration of conditioned reflexes.

3. *After conditioning.* The authors distinguish two processes which after conditioning, are able to inhibit positively conditioned reflexes:

(*a*) conditioned inhibition — corresponding to inhibition of extinction, differentiation and delay — which depends on a temporary depression of the thalamo-cortical projection system previously activated by the conditioned stimulus;

(*b*) unconditioned inhibition — corresponding to external or supra-maximal inhibition — which depends on a temporary depression of the brain stem reticular system. This depression may become generalised over the brain by means of diffuse ascending projections.

Editorial Note: This article was originally submitted as three manuscripts, which were condensed into this single paper.

BIBLIOGRAPHIE

ABE, M. Electrical responses of the human brain to acoustic stimulus. *Tohoku J. Exp. Med.*, **1954**, *6*: 47-58.

ADRIAN, E. D. Afferent discharges to the cerebral cortex from peripheral sense organs. *J. Physiol.*, **1941**, *100*: 159-191.

BEKHTEREVA, . Caractéristique électro-physiologique des processus réflexo-conditionnels chez des malades souffrant de tumeurs ou d'affections tumorales du cerveau. *Rev. Physiol.* (Léningrad), **1955**, XLI, *2*: 187.

BERITCHAVILI et VOROBIEV, **1943**, cité par MAIORTCHIK et SPIRINE, **1951**.

CLAES, E. Contribution à l'étude physiologique de la fonction visuelle. Analyse oscillographique de l'activité spontanée et sensorielle de l'aire visuelle corticale chez le chat non anesthésié. *Arch. Int. Physiol.*, **1939**, *48*: 181-237.

DONGIER, S., GASTAUT, Y. et DONGIER, M. Enregistrement polygraphique de l'effet de surprise. Relations entre les résultats obtenus et les données cliniques. *Colloque Marseille 1955*, Masson & Cie Ed. Paris, **1957**.

DURUP, G. et FESSARD, A. L'électroencéphalogramme de l'homme. *L'année Phychol.*, **1935**, *36*: 1-32.

GASTAUT, H. Etude électrocorticographique de la réactivité des rythmes rolandiques. *Rev. Neurol.*, **1952**, 87, *2*: 176-182.

GASTAUT, H. Les machines à calculer et le cerveau humain. *C. R. Colloque Int. C.N.R.S.*, Paris, **1953**, : 447-459.

GASTAUT, H. and BERT, J. EEG changes during cinematographic presentation. *EEG Clin. Neurophysiol.*, **1954**, *6*: 433-444.

HAGBARTH, K. E. and KERR, D. I. B. Central influences on spinal afferent conduction. *J. Neurophysiol.*, **1954**, *17*: 295-307.

HERNÁNDEZ-PEÓN, R. and SHERRER, H. ''Habituation'' to acoustic stimuli in cochlear nucleus. *Fed. Proc.*, **1955**, *14*: 71.

IWAMA, K. Delayed conditioning in man and brain waves. *Tohoku J. Exp. Med.*, **1950**, *52*: 53-63.

IWAMA, K. and ABE, M. Electroencephalographic study of conditioned salivary reflex in human subjects. *Tohoku J. Exp. Med.*, **1952**, *56*: 345-355.

IWAMA, K. and ABE, M. Conditioned galvanic skin reflex and electroencephalogram. *Tohoku J. Exp. Med.*, **1952**, *57*: 327-335.

JASPER, H. H. Diffuse projection systems: the integrative action of the thalamic reticular system. *EEG Clin. Neurophysiol.*, **1949**, *1*: 405-419.

JASPER, H. H. and AJMONE-MARSAN, C. Thalamo-cortical integrating mechanisms. *Res. Publ. Ass. nerv. ment. Dis.*, **1952**, *30*: 493-512.

JASPER, H. H. and CRUIKSHANK, R. M. Electroencephalography: II. Visual stimulation and the after image as affecting the occipital alpha rhythm. *J. Gen. Psychol.*, **1937**, *17*: 29-48.

JASPER, H. H., NAQUET, R. and KING, E. E. Thalamus cortical recruting responses in sensory receiving areas in the cat. *EEG Clin. Neurophysiol.*, **1955**, *7*: 99-114.

JASPER, H. H. and PENFIELD, W. Electrocorticograms in man: Effect of voluntary movement upon the electrical activity of the precentral gyrus. *Arch. für Psych. und Zeits. Neurol.*, **1949**, *183*: 163-174.

JASPER, H. H. and SHAGASS, C. Conditioning the occipital alpha rhythm in man. *J. Exper. Psychol.*, **1941**a, *26*: 373-388.

JASPER, H. H. and SHAGASS, C. Conscious time judgements related to conditioned time intervals and voluntary control of the alpha rhythm. *J. Exper. Psychol.*, **1941**b, *28*: 503-508.

JOUVET et HERNÁNDEZ-PEÓN, R. Mécanismes neurophysiologiques concernant l'attention, l'habituation et le conditionnement. *Colloque Marseille 1955*, Masson et Cie Ed., **1957**.

JUS, A. et C. Essai d'analyse électroencéphalographique des processus d'inhibition interne (le retard et son passage au sommeil). *Rev. Neuropathol. Psychiat.*, Moscou, **1954**, *9*: 715-720.

KING, E. E. Differential action of anesthetics and interneurons depressants upon EEG arousal and recruiting responses. *J. Pharmacol. exp. ther.*, **1956**, *116*: 408-418.

KING, E. E., NAQUET, R. and MAGOUN, H. W. Alterations in somatic afferent transmission through thalamus by central mechanisms and barbiturates. *J. Pharmacol. exp. Therap.*, **1956**, in press.

KNOTT, J. R. and HENRY, C. E. The conditioning of the blocking of the alpha rhythm of the human electroencephalogram. *J. Exp. Psychol.*, **1941**, *28*: 134-144.

KOJEVNIKOV et MAROUSSEVA, **1949**, cité par MAIORTCHIK et SPIRINE, **1951.**

LINDSLEY, D. B., BOWDEN, J. and MAGOUN, H. W. Effect upon the EEG of acute injury to the brain stem activating system. *EEG Clin. Neurophysiol.*, **1949**, *1*: 475-486.

LISSAK. Nouveaux aspects expérimentaux dans l'étude des mécanismes diencéphaliques des processus de l'Activité nerveuse supérieure. *Rev. Act. Nerv. Sup. I. P. Pavlov*, **1955**, Moscou, 5. No *5*.

LIVANOV, M. K., KOROLKOVA, I. A. et FRENKEL, G. M. Recherches électrophysiologiques sur l'activité nerveuse supérieure. *Rev. Act. nerv. Sup. I. P. Pavlov*, **1951**, Moscou, 1, No *4*.

LOOMIS, A. L., HARVEY, E. N. and HOBART, G. A. Electrical potentials of the human brain. *J. Exper. Psychol.*, **1936**, *19*: 249-279.

MAIORTCHIK, V. E. et SPIRINE, B. G. Analyse électrophysiologique des processus corticaux au cours de la formation de la liaison temporaire chez l'homme. In *Problèmes de Neuro-Chirurgie*, **1951**, Moscou, *3*: 3-11.

MAGNUS, O. The central alpha rhythm (''rythmes en arceau''). *EEG Clin. Neurophysiol.*, **1954**, *6*: 349-350.

MORRELL, F. et NAQUET, R. Conditionnement électrocorticographique chez le chat normal et épileptique. *Congrès Int. Physiol.*, **1956**, in press.

MORRELL, F. and ROSS, M. Central inhibition in cortical conditioned reflexes. *Arch. Neurol. Psychiat.*, Chicago, **1953**, *70*: 611-616.

MORUZZI, G. and MAGOUN, H. W. Brain stem reticular formation and activation of the EEG. *EEG Clin. Neurophysiol.*, **1949**, *1*: 455-473.

MOTOKAWA, K. Electroencephalograms of man in the generalisation and differenciation on conditioned reflexes. *Tohoku J. Exp. Med.*, **1949**, *50*: 225-234.

MOTOKAWA, K. and HUZIMORI, B. Electroencephalograms and conditioned reflexes. *Tohoku J. Exp. Med.*, **1949**, *50*: 215-223.

OUKHTOMSKI cité par ROUSSINOV, S. in: Les théories de Vvedensky et Oukhtomsky sur l'inhibition et leurs rapports avec celles de Pavlov. *Rev. Act. Nerv. Sup.*, Moscou, **1955**, *3*: 305-318.

PAVLOV, B. cité par SMIRNOV. *Colloque de Marseille 1955*, Masson et Cie Ed., Paris, **1957.**

PAVLOV, I. P. Leçons sur le travail des hémisphères cérébraux. Amédée Legrand, Paris, **1929.**

POPOV, C. Contribution à l'étude des fonctions corticales chez l'homme: VI. Inhibition externe étudiée par la méthode électroencéphalographique et la méthode des images consécutives. *C. R. Acad. Sc.*, **1954**, *239*: 1859-1862.

POPOV, C. Inhibition corticale et arrêt des ondes alpha étudiées au point de vue de la physiologie cérébrale pavlovienne. *Ann. Med. Psychol.*, 113ème Année, II: 461-473.

ROGER, A., ROSSI, G. F. et ZIRONDOLI, A. Le rôle des afférences des nerfs crâniens dans le maintien de l'état vigile de la préparation ''encéphale isolé''. *EEG Clin. Neurophysiol.*, **1956**, *8*: 1-13.

ROUSSINOV, S. Les théories de Vvedensky et Oukhtomsky sur l'inhibition et leurs rapports avec celles de Pavlov. *Rev. Act. Nerv. Sup. I. P. Pavlov*, **1955**, *3*: 305-318.

SHAGASS, C. *Master's Thesis.* Dep. of Psychology. University of Rochester, **1941.**

SHAGASS, C. and JOHNSON, E. P. The course of acquisition of a conditioned response of the occipital alpha rhythm. *J. Exp. Psychol.*, **1943**, *33*: 201-219.

SKIPINE. Localisation du processus d'inhibition conditionnelle chez le chien. *Rev. Act. Nerv. Sup.*, Moscou, **1956**, Vol. *50*.

SPILBERG. **1937**, cité par MAIORTCHIK et SPIRINE, **1951.**

STARZL, T. E., TAYLORS, C. and MAGOUN, H. W. Collateral afferent excitation of reticular formation of brain stem. *J. Neurophysiol.*, **1951**, *14*: 479-496.

STORM VAN LEEUWEN, W., BEKKERING, D. H., KAMP, A., DE LANGE, J. et WERRE, J. P. Corrélations entre quelques phénomènes psychologiques et l'activité électrique cérébrale. *Colloque Marseille 1955*, Masson et Cie Ed. Paris, **1957.**

TCHOUGOUNOV, S. H. Importance de l'électroencéphalographie pour le diagnostic des troubles de l'activité nerveuse supérieure en clinique. *Rev. Neuropath. Psychol.*, Moscou, **1952**, *1*: 26-33.

TRAVIS, L. I. and EGAN, J. B. Conditioning of the electrical response of the cortex. *J. Exp. Psychol.*, **1938**, *22*: 524-531.

VERDEAUX, G. et J. et FRANCES, R. L'enregistrement polygraphique dans la perception visuelle et auditive. *Colloque de Marseille, 1955*, Masson et Cie Ed., Paris, **1957.**

VVEDENSKY cité par ROUSSINOV, S. in: Les théories de Vvedensky et Oukhtomsky sur l'inhibition et leurs rapports avec celles de Pavlov. *Rev. Act. Nerv. Sup.*, Moscou, **1955**, *3*: 305-318.

WALTER, W. G. and V. J. Central effects of sensory stimulation. *EEG Clin. Neurophysiol.*, **1949**, *1*: 57-86.

YOSHII, N. Methodological principles of electroencephalographic investigation on conditioned behaviour. *Colloque de Marseille, 1955*, Masson et Cie, Ed., Paris, **1957.**

YOSHII, N., PRUVOT, P. et GASTAUT, H. A propos d'une activité rythmique transitoirement enregistrée dans la formation réticulée mésencéphalique et susceptible de représenter l'expression électroencéphalographique de la trace mnémonique. *C. R. Acad. Sc.*, **1956**, *242*: 1361-1364.

Reference: GASTAUT, H., JUS, A. et C., MORRELL, F., STORM VAN LEEUWEN, W., DONGIER, S., NAQUET, R., REGIS, H., ROGER, A., BEKKERING, D., KAMP, A. et WERRE, J. Etude topographique des réactions électroencéphalographiques conditionnées chez l'homme. *EEG Clin. Neurophysiol.*, **1957**, *9*: 1-34.

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THE ELECTRICAL RESPONSES OF THE UNANAESTHETISED AUDITORY CORTEX IN THE INTACT CAT

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Studies of the electrical behaviour of the auditory cortex have been made either under anaesthesia of various depths (Woolsey and Walzl 1942; Tunturi 1944, etc.), or on the unanaesthetised "encéphale isolé" (Bremer and Bonnet 1949; Bremer 1943). In view of the work of Moruzzi and Magoun (1949) and others it is evident that the cortex in the "encéphale isolé" and "cerveau isolé" is in a condition which is far from normal. It is of interest therefore to study the behaviour of the auditory cortex in the intact conscious animal.

METHODS

Cortical electrodes were implanted in cats, following the technique of Bradley and Elkes (1953). Six silver electrodes, with tips about 0.5 mm. in diameter were implanted in three pairs, "domino-fashion", over the primary auditory area so as to be just resting on the cortical surface. The electrodes were spaced 5-6 mm. apart with the long axis of the array roughly parallel with the mid-part of the suprasylvian sulcus and the more medial row of electrodes lying along the middle ectosylvian gyrus. Two "indifferent" electrodes made contact with the bone of the skull over the frontal sinus. In some experiments additional electrodes were implanted over other cortical areas. Leads from the electrodes were brought out to a multiple-way socket carried on a harness on the cat's shoulders. The animals were allowed a week to recover after operation before any recordings were made; the preparations remained in good condition and were kept for periods of up to several months.

During recording the cat was kept in a sound-insulated box, 4 ft. × 2 ft. × 2 ft. lined with absorbent material, and had a sufficient length of lead attached to allow it to move freely within this space. The output from the electrodes was recorded by means of a standard 4-channel physiological amplifier and pen recorder (Ediswan).

Impulsive or tonal stimuli were delivered by applying the appropriate electrical signal to a loudspeaker in the roof of the box; mechanical "clappers" were also employed. Frequency-modulated tones were generated by means of an audio-frequency oscillator whose frequency was varied about a central value by means of a velodyne-driven rotating capacitor. Thus the central frequency, depth of modulation, and modulation rate could each be independently controlled. The modulation envelope was recorded simultaneously with the cortical traces by utilizing the signal from a generator driven from the same shaft as the modulating capacitor. Precautions were taken to maintain the amplitude of the output completely constant during the modulation cycle. Some difficulty was experienced with standing wave patterns in the original experiments, even with a sound absorbent lining, but this was overcome by the fitting of diagonally placed absorbent baffles. In the final arrangement, the sound intensity did not vary by more than 1 db. at any one point in space over the modulation range used.

RESULTS

Records from the unanaesthetised auditory cortex in the intact animal are shown in figure 1. The response to an impulsive stimulus (click) is also shown in the same figure, and is seen to consist of a sharp surface-positive wave followed by a slower surface-negative wave, essentially similar to that found by Bremer in the "encéphale isolé" and indeed in the lightly anaesthetised animal.

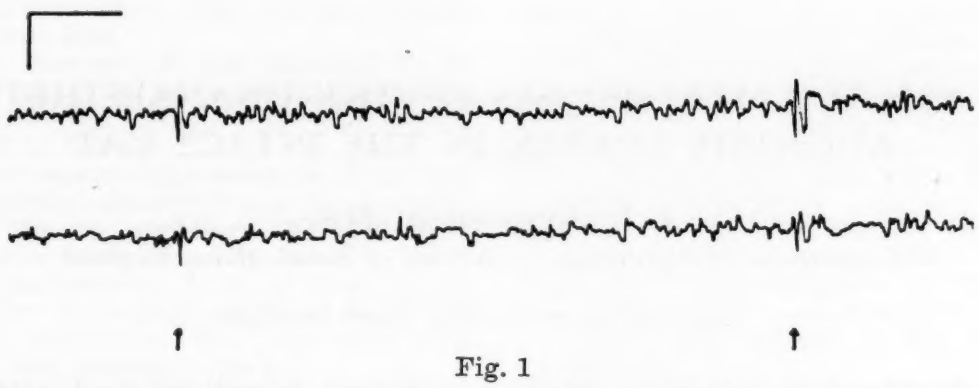

Fig. 1

Unipolar records from two points on the middle ectosylvian gyrus. "Click" stimuli applied at the arrows. Calibration, 1 sec. and 100 μV. "Indifferent" electrodes in bone over frontal sinus.

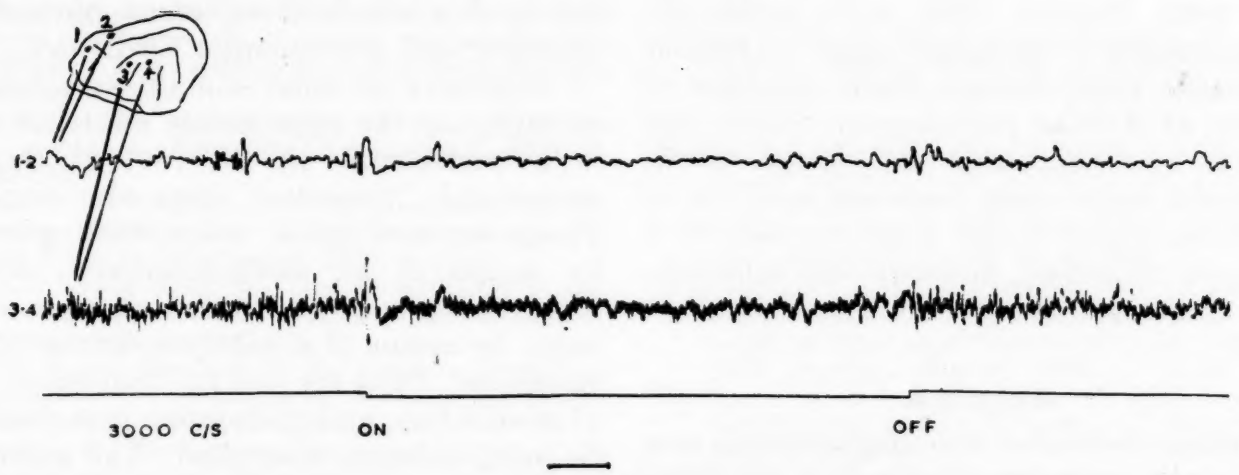

Fig. 2

Effect on the cortical response of stimulation with a tone of 3000 c/sec. Three-4 response from primary auditory area; 1-2 response from non-auditory region. Time-bar 1 sec.

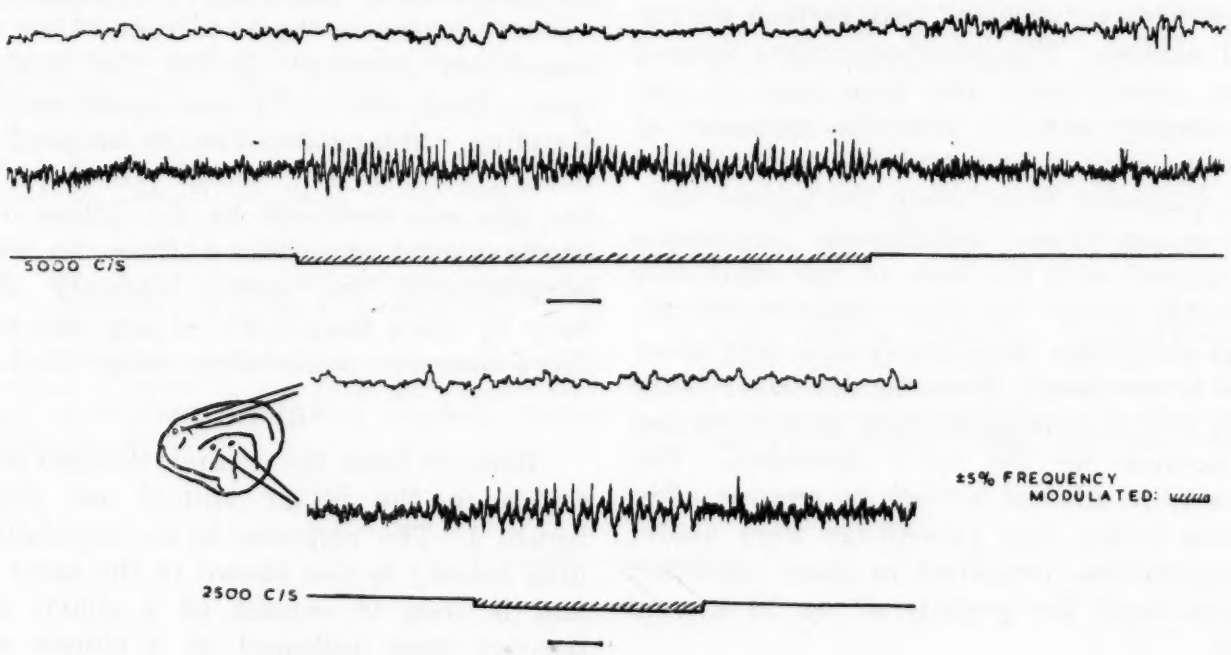

Fig. 3

Response of auditory cortex to frequency modulated tones. The tones are sounded steadily at the indicated frequencies except during the shaded period on the signal trace when they are modulated $\pm$ 5 per cent of the central frequency at a few cycles per sec. The frequency of the major response corresponds to the modulation frequency.

A second, even slower, surface-positive deflection appears immediately after the negative deflection.

The response to a pure tone stimulus is seen in figure 2. The medium amplitude activity of the resting record is replaced by lower amplitude fast activity. Sometimes this is seen only for a short time after the onset of the stimulus and the record then returns to something essentially indistinguishable from the unstimulated state. Possibly this depends on the "set" of the reticulo-thalamo-cortical system. The response to a tonal stimulus with regular high-frequency waves of large amplitude compared with the resting record, observed by Bremer (1943) in the "encéphale isolé", has not been seem by us in the intact animal.

It is well known that rhythmic repetition of a sensory stimulus, that is to say an amplitude modulated stimulus, will elicit at the cortex a corresponding rhythm. This has been particularly well studied in the visual system with flicker experiments. The analogous effect can be obtained in the auditory cortex.

As pointed out in an earlier communication (Whitfield 1953), a similar response can be obtained if the intensity of a tone is held constant but the *frequency* varied rhythmical-

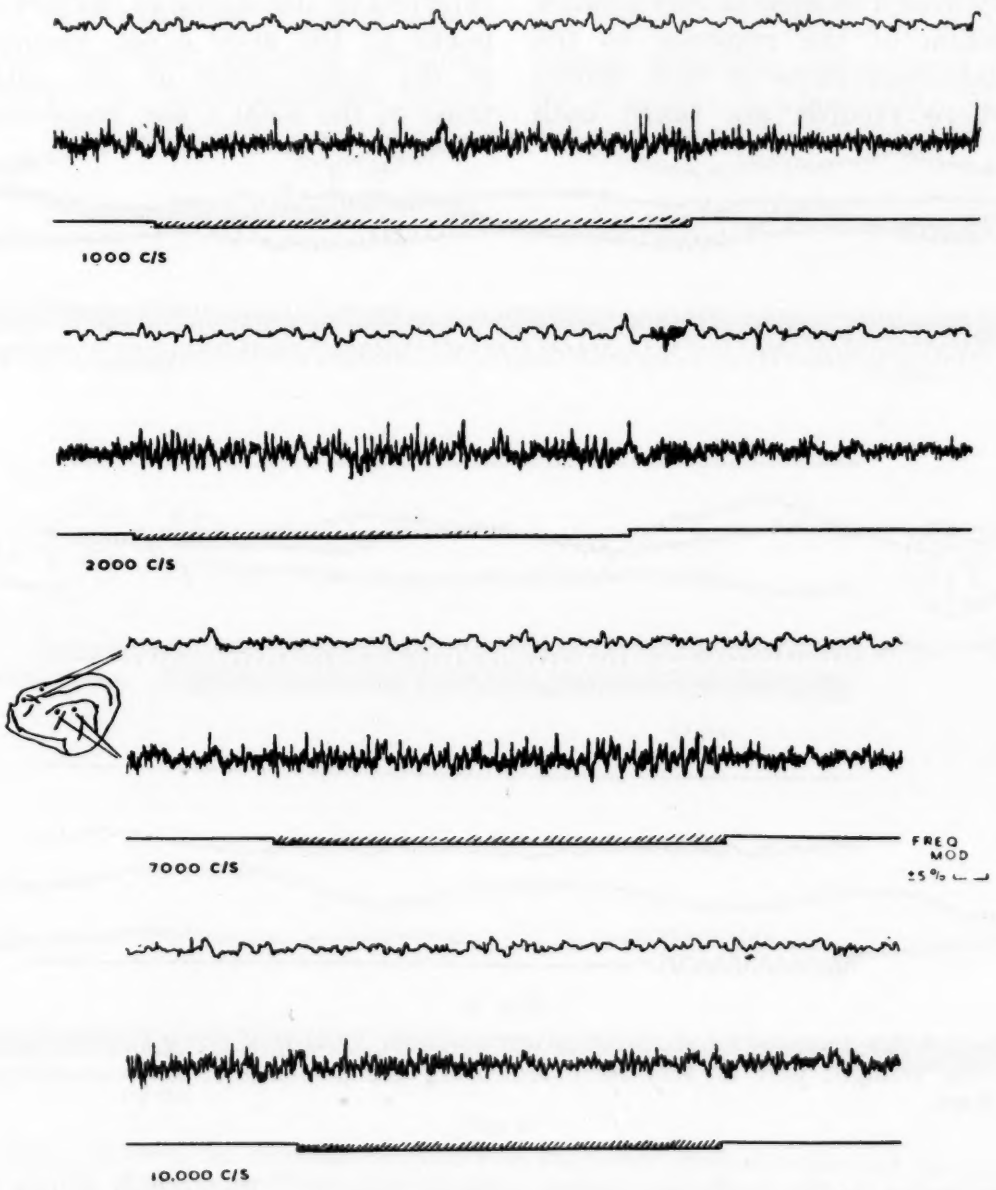

Fig. 4

Range over which response is obtained from one electrode. Same experiment as figure 3. Response just visible at 2000 c/sec. and 7000 c/sec.

ly. Under these conditions a strong component at the frequency of the modulation envelope appears in the record (fig. 3). The depth of modulation required is quite small, ± 5 per cent of the central frequency being adequate to show the effect. Some response is obtained from a given electrode over a wide range of frequency (fig. 4), although it is well-marked only over a comparatively smaller band. The relation of the response to the stimulus modulation-envelope is well shown in figure 5, where records are taken both

In some experiments two maxima have been observed in the response as the central frequency is varied. Thus in one case maximal responses were obtained at 4000 c/sec. and 5500 c/sec. with a reduced response at intermediate values. Furthermore the general phase of the response at 4000 c/sec. tended to differ from that at 5500 c/sec. by 180° when referred to the stimulus envelope, the positive peaks of the 4000 c/sec. response occurring at the upper limit of the modulation, and those of the 5500 c/sec. response at the lower

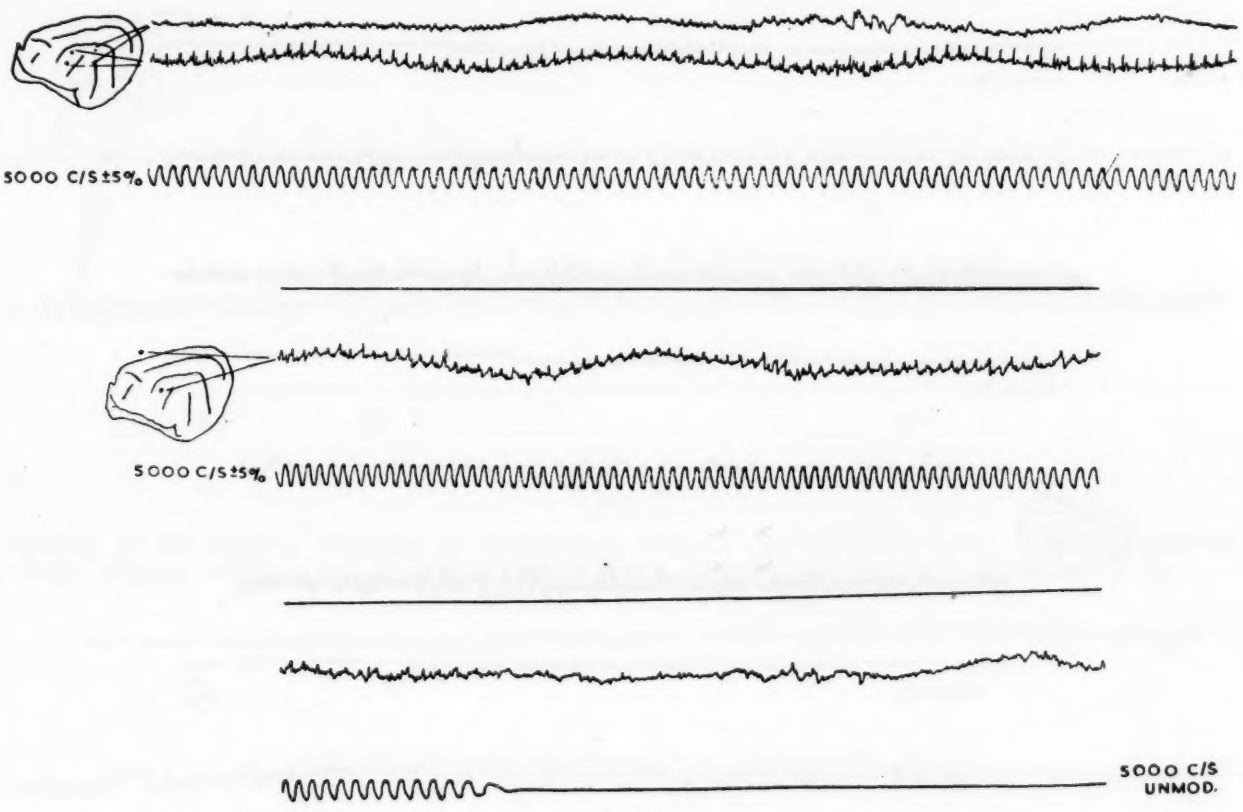

Fig. 5

The relation of the response to the modulation envelope. Lower trace shows the modulation waveform, the straight part of this trace indicating the presence of an unmodulated tone. Time-bar, 1 sec.

between two electrodes on the auditory cortex, and between one such electrode and an "indifferent" electrode. The cessation of the response, when the modulation is removed but the tone continued, is clearly seen. The record also demonstrates the absence of any response from a non-auditory region. The response corresponding to the modulation envelope is obtained equally well over a wide range of modulation frequency; the frequency of the modulator used could be varied between 2 and 18 c/sec., and responses were obtained throughout this range (fig. 6).

limit (fig. 7). The effect is not dependent on the modulation rate. This would suggest that the respective activities occupy different spatial positions on the cortical surface.

DISCUSSION

The responses of the primary auditory cortex in the intact unanaesthetised cat differ from those obtained from the anaesthetised and "encéphale isolé" preparations, especially when tonal stimuli are used. Moreover, there is some variation in the response obtained at different times from the same

preparation with similar stimuli. Thus the reaction of even the primary projection area is apparently considerably modified by other variables, and the effects of stimulation, though more marked, are much less certainly reproducible than under conditions of anaesthesia. The least variation is seen in the type of response least affected by anaesthesia, that is the ''click'' response. This is easily elicited, and the electrical response obtained is initially similar to those obtained under light anaesthesia or in the ''encéphale isolé''.

Attempts to record the response to tonal stimulation under simple anaesthesia have not yielded very clear results; such experiments have been carried out by Tunturi (1944) on the dog, but results were obtained only with onset tones. Good local responses have been obtained from anaesthetised cortex however after treatment of the surface with strychnine (Tunturi 1950; Hind 1953). The response of the unanaesthetised cortex has been studied in the ''encéphale isolé'' by Bremer and his school (Bremer and Bonnet 1949; Bremer 1943), who found regularisation and acceleration of the spontaneous potential waves, accompanied sometimes by an increase, sometimes by a decrease, in the amplitude of response.

In the intact animal the typical response is that of figure 2, where the stimulus causes the resting activity to be replaced by a low-voltage irregular fast activity. At other times the stimulus is apparently ''ignored'', there being little change, or only a transient change, in the resting record. The increased amplitude regular oscillation observed by Bremer in the ''encéphale isolé'' has never been observed in the intact animal. However, in view of the difference in status between the ''encéphale isolé'' and the intact animal, in which the afferents to the reticular formation appear to play a part (Moruzzi and Magoun 1949), differences in response are not altogether surprising.

While the response to steady tones does not

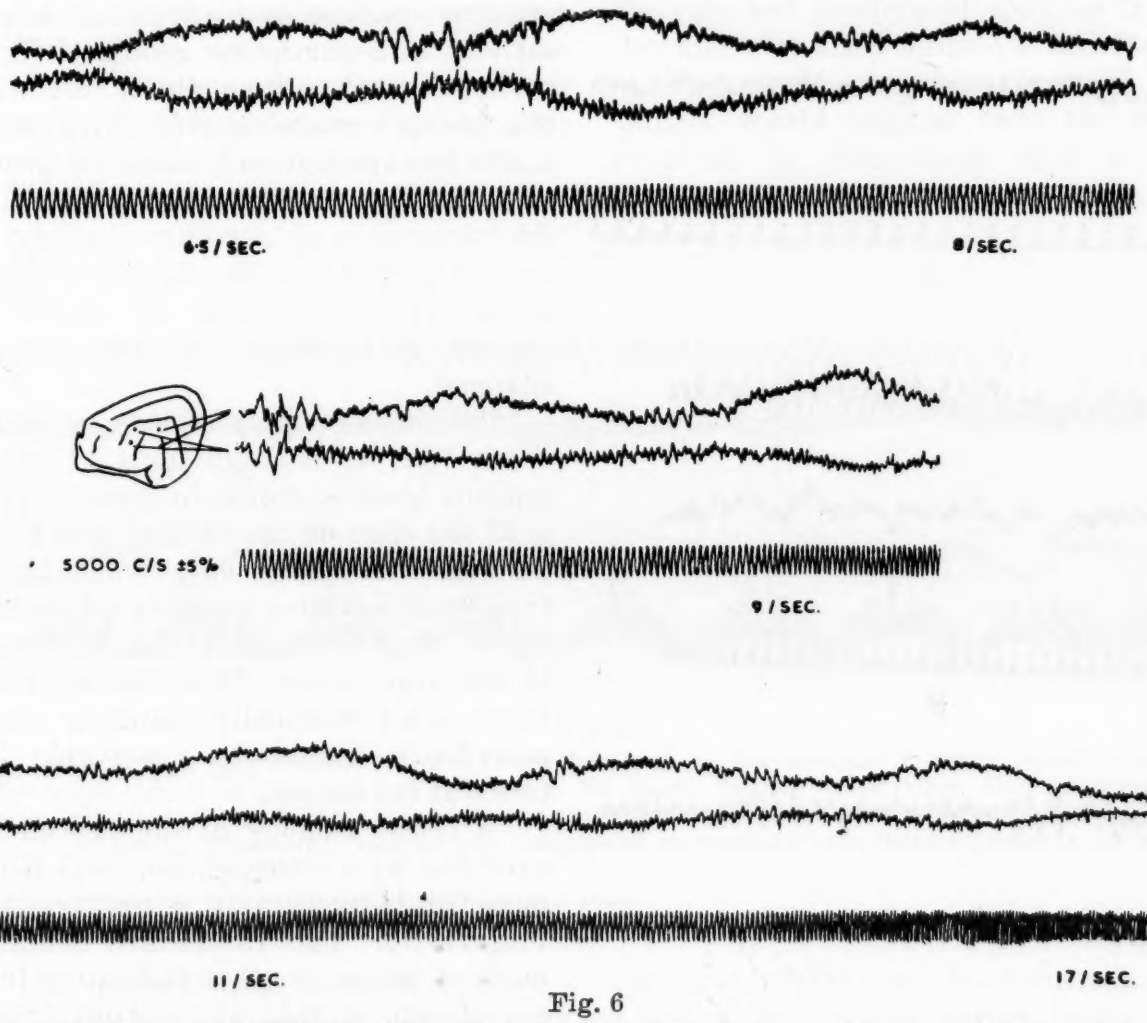

Fig. 6

Correspondence between the response frequency in the lower cortical trace and the modulation frequency of the stimulus is shown over a wide range.

show any very striking properties when recorded with gross electrodes, the response to tones whose frequency is varied rhythmically over a small range is markedly different. The auditory cortex responds to such stimuli with a wave containing a strong component at the frequency of modulation of the stimulus. The range of central frequency over which such a response can be obtained is fairly large, and suggests, in spite of the effects due to current spread, that the area activated by a given stimulus is appreciable, and not situated at a point.

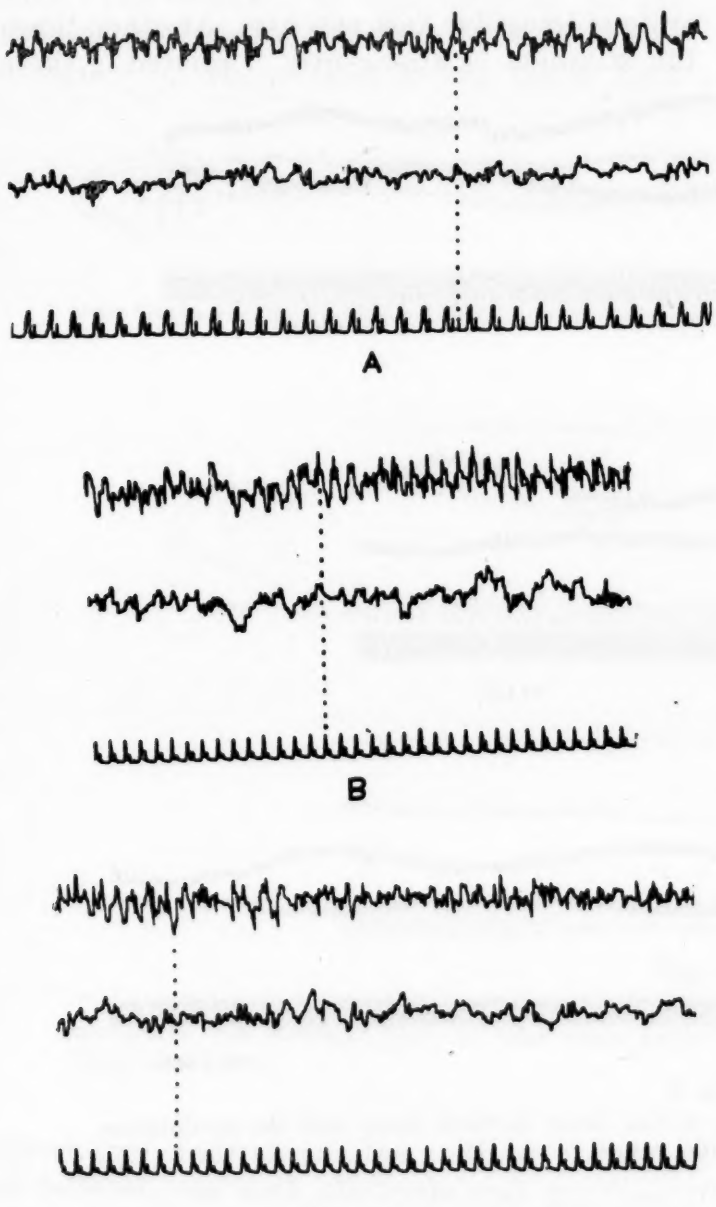

Fig. 7

Phase difference in the response to a sinusoidally frequency-modulated tone. A. Centre frequency 4000 c/sec., modulation rate 4 c/sec. B. Same electrodes, centre frequency 5500 c/sec., modulation rate 6 c/sec. C. Same electrodes, centre frequency 4000 c/sec., same modulation rate as B.
"Unipolar" recordings from middle ectosylvian gyrus. The peak of the signal marks the instant at which the modulation envelope reaches the point of maximum deviation towards the high frequency side.
The labile nature of the response is well illustrated by the second half of record C.

The work of Woolsey and Walzl (1942) and of Tunturi (1944) demonstrated an orderly projection of the fibres of the spiral lamina upon the cortex. It has been shown by Hilali and Whitfield (1953) that the lower levels of the auditory pathway act upon the sensory input so as to produce near-maximal activity in a particular group of fibres in response to a pure tone, the fibres adjacent to this group remaining effectively inactive. It might be expected on anatomical grounds that this activity pattern would be reflected in the occurrence of a rather sharply delimited area of activity on the cortex. Further, such an active area would, of course, tend to change its position as the frequency is changed.

The effect of frequency modulation on the output of a single unit at the cochlear nucleus level is shown in figure 8. This unit is at the edge of the excited array and forms part of that array only when the stimulus frequency deviates towards its lower limiting value. A similar situation exists, of course, at the lower edge. Thus the active group of fibres is a periodically changing one, and this periodicity should be observable in spatial terms at the cortex.

A crude analogy of the expected effect is provided by a series of electrical filters whose pass bands overlap in a progressive manner (figure 9). The filters are connected to a bank of lamps or other indicators in the manner shown, so that any output from a given filter causes its lamp to glow. Then if the stimulating frequency sweeps through the range covered by the set of filters a certain number of lamps will always be illuminated but the position of the illuminated block will change as the frequency is changed.

The movement of the "edge" past the electrode region on the cortex would result in a sharp change in the electrical potential. The existence of such a moving region of uniform excitation receives support from observations of the responses with different central frequencies and the same electrode array. If, for simplicity, we assume a linear distribution

of frequency along a line on the cortical surface, and an electrode located somewhere in the centre of the region, then if the centre of the active region is "above" (in the frequency sense) the electrode position, the nearer edge will approach that position as the frequency falls; conversely, if the active region is "below" the electrode position, then the edge will approach it as the frequency rises. Thus we should expect a phase difference of 180° between corresponding deflections in the two cases, relative to the modulation envelope. Furthermore, if the active region has a plateau (as theory predicts) then for a frequency whose activity is located under the electrode position there should be minimal activity — provided the excursion is not too large — since the active region remains permanently under the electrode. We have obtained some evidence in recent experiments that such a pattern of response does occur, there being separate maxima which show a difference in phase when compared with the stimulus (fig. 7). While the recording technique and electrode distribution employed do not enable any very detailed conclusions to be drawn for the phase data, the general effect is consistent with the proposed hypothesis.

It is true that these results would be equally explicable in terms of a "double-hump" response, in which there were regions of activity corresponding only to the edges of the active array demonstrated at lower levels, and zero or reduced activity in the region corresponding to the central part of the afferent fibre array — rather than in terms of an active plateau. These questions can only be resolved by more detailed studies of the phase relations of the cortical activity at closely-spaced points, and such studies are now in progress. The collection of data is further complicated by the labile nature of the responses already referred to, the amplitude of the relevant component varying from day to day and even from minute to minute.

The results on phase reversal so far obtained, would suggest that the active area involved by stimulation with tones in the region of 3-6000 c/sec. is of the order of "1000 c/sec. wide", which agrees fairly well with the bandwidth of the active fibre arrays deduced from tonal response experiments at the trapezoid body level (Allanson and Whitfield 1956) and from the tonal inhibition results of Erulkar (1955) at the midbrain level. The bandwidth is dependent on intensity, at these levels, and intensity changes would therefore also presumably affect the cortical response in a similar way, but the general agreement is good.

Since it may be the boundary regions between active and inactive parts of the system which are significant, rather than the centre of the active region, this may possibly

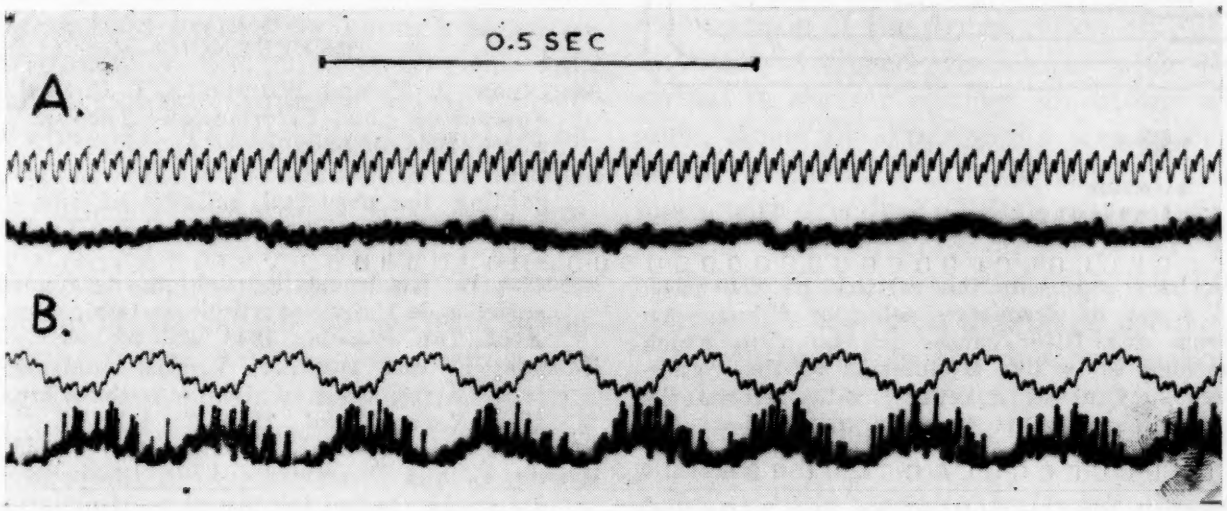

Fig. 8

Response from a single unit in the efferent pathway of the cochlear nucleus (lower traces). The upper trace in each record exhibits a 50 c/sec. timing wave when the fundamental stimulating tone is switched on, and has superimposed on it the modulation waveform when the fundamental is frequency modulated. Downward movement of the trace represents deviation toward a lower frequency.
(A) No response to an unmodulated 200 c/sec. tone.
(B) Response when the same tone is frequency modulated at 6 c/sec. over a range of 200 c/sec.

serve to explain some of the anomalies which have been found between the cortical frequency locations determined by direct stimulation and by strychnine on the one hand, and the results of cortical ablation on the other. A lesion placed in the centre of the

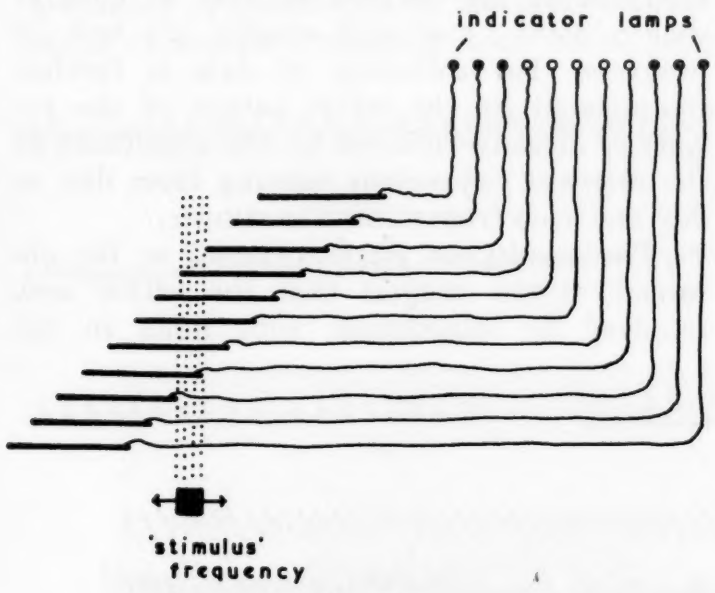

Fig. 9

The thick bars represent the relation of the pass-bands of a set of frequency selective filters. An output from any filter causes the lamp to which it is connected to be lit. Modulation of the "stimulus" frequency about a central value causes the block of illuminated lamps to move up and down the array.

active region may not produce the expected result unless extensive enough to involve both edges of the array. While it is not suggested that the determination of pitch in terms of the relation between two boundaries rather than in terms of a strictly tonotopic point distribution, resolves the anomalies which have been found, it would seem worth while re-examining the effect of ablation in terms of this possibility.

SUMMARY

1. The electrical responses of the unanaesthetised auditory cortex in the intact animal differ from those in the anaesthetised and "encéphale isolé" preparations.

2. Responses to stimulation show considerable variability, "click" responses being most stable.

3. A cortical response which contains a component at the modulation frequency is obtained with frequency modulated stimuli.

4. Examination of this response, taken with the results at lower neural levels, suggests that an extensive, but rather sharply delimited area is activated by each tone and that this area moves across the cortex as the stimulating frequency is changed.

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REFERENCES

ALLANSON, J. T. and WHITFIELD, I. C. *3rd London Symposium on Information Theory.* Butterworth, **1956**, 269-286.

BRADLEY, P. B. and ELKES, J. A technique for recording the electrical activity of the brain in the conscious animal. *EEG Clin. Neurophysiol.*, **1953**, *5*: 451-456.

BREMER, F. Etude oscillographique de réponses sensorielles de l'aire acoustique corticale chez le chat. *Arch. Int. Physiol.*, **1943**, *53*: 53-103.

BREMER, F. and BONNET, V. An analysis of the sensory responses of the acoustic cortex. *EEG Clin. Neurophysiol.*, **1949**, *1*: 447-449.

ERULKAR, S. Personal communication, **1955**.

HILALI, S. and WHITFIELD, I. C. Responses of the trapezoid body to acoustic stimulation with pure tones. *J. Physiol.*, **1953**, *122*: 158-171.

HIND, J. E. An electrophysiological determination of tonotopic organisation in auditory cortex of cat. *J. Neurophysiol.*, **1953**, *16*: 475-489.

MORUZZI, G. and MAGOUN, H. W. Brain stem reticular formation and activation of the EEG. *EEG Clin. Neurophysiol.*, **1949**, *1*: 455-473.

TUNTURI, A. R. Audio frequency localization in the acoustic cortex of the dog. *Amer. J. Physiol.*, **1944**, *141*: 397-403.

TUNTURI, A. R. Physiological determination of the arrangement of the afferent connections to the middle ectosylvian auditory area in the dog. *Amer. J. Physiol.*, **1950**, *162*: 489-502.

WHITFIELD, I. C. Auditory nerve patterns and their relation to the cortical response. *Abstr. XIX int. physiol. Congr.*, **1953**, p. 885.

WOOLSEY, C. N. and WALZL, E. M. Topical projection of nerve fibres from local regions of the cochlea to the cerebral cortex of the cat. *Johns Hopk. Hosp. Bull.*, **1942**, *71*: 315-344.

Reference: WHITFIELD, I. C. The electrical responses of the unanaesthetised auditory cortex in the intact cat. *EEG Clin. Neurophysiol.*, **1957**, *9*: 35-42.

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THE ACTION OF ANTICONVULSANT DRUGS TESTED BY ELECTRICAL STIMULATION OF THE CORTEX, DIENCEPHALON AND RHINENCEPHALON IN THE UNANESTHETIZED RABBIT

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Although the mechanisms of epilepsy have been extensively investigated in the past years, the action of anticonvulsant drugs has not been determined accurately enough to correlate satisfactorily the pharmacological data with the present neurophysiological conceptions of epilepsy. The testing of drugs by observing their effect on convulsions induced by electroshock or Metrazol injections provides only general information about the efficiency of a drug, but does not allow determination of its action on definite structures of the brain. On the other hand, the mere analysis of the motor seizure pattern before and after administration of a drug gives little information about its action, since electrical discharges may occur without any corresponding motor phenomena.

The aim of the present paper was to determine more precisely the action of some clinically well known anti-epileptic drugs by means of strictly localized electrical stimuli in the chief cerebral structures (cortex, diencephalon and rhinencephalon). The electrographic responses induced by these stimuli might show significant alterations under the influence of a drug and allow determination of its site of action, especially if the stimulation was applied, as in our method, to an unanesthetized animal. Since we stimulated not only the cortex, like previous investigators, but also the diencephalon and the rhinencephalon, we were able to compare the topographic alterations induced by the anticonvulsant drugs in the animal with the action of those drugs on the clinically familiar cortical, diencephalic and rhinencephalic seizures in man. Comparison of the drugs action on our experimentally induced discharges with that observed in similar clinical conditions was possible, since all experiments were carried out on unanesthetized animals hanging in a hammock with freedom of limb movement.

The electrographic response of a brain structure to electrical stimulation with liminal voltage consists of a discharge occuring during the stimulation and of a self-sustained after-discharge outlasting the end of the stimulus by a certain time. As a criterion for pharmacological analysis we chose, in this series of experiments, the after-discharge, since it corresponds closely to the prolonged paroxysmal EEG patterns recorded during seizures in human epilepsy and since the duration of the after-discharge may be measured in seconds from the end of the stimulus.

METHOD

A detailed description of our experimental method has already been given elsewhere (Gangloff and Monnier 1955) and may be briefly summarized here: a stereotaxic socklet is screwed on the skull of the rabbit under local anesthesia. The varnish-insulated electrode for electrical stimulation consists of 6 steel needles of 3 different lengths. The 1 mm. long bare needle-tips are implanted in the cortex, in the lateral thalamus, in the dorsal or in the ventral rhinencephalon of the right hemisphere (fig. 1). Stimuli, shaped like action-potentials in peripheral nerve, are provided by a Wyss stimulator (1950). Im-

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pulse duration of 1.0, 3.3 or 7.0 msec. and frequencies of 30 or 40 imp/sec. are used. The stimulus is applied for 10-15 sec. The location of the stimulated point is controlled anatomically. Traumatically injured points are not taken into consideration.

The cortical electrical activities are derived by means of epidural silver electrodes screwed into the skull above the sensorimotor cortex and the occipital (visual) cortex of both hemispheres. For the detection of subcortical activities, varnish insulated needle electrodes are used, the free tips of which are located in the lateral and medial thalamus, in the dorsal rhinencephalon and in the midbrain reticular formation of the left hemisphere (fig. 1). The spontaneous and electrically induced activities of these structures are recorded with a Grass 6-channel inkwriter and, more recently, with a 12-channel Schwarzer electroencephalograph.

At the beginning of the experiment, the threshold of the after-discharge is determined in the cortex, diencephalon (thalamus) and rhinencephalon. The same determination is repeated 1½ hours, 3 and 4½ hours after oral administration of the drug. In addition to the threshold in volts, the duration of the after-discharge in seconds and the electrographic pattern itself are chosen as parameters. The alterations of these parameters occurring during 4½ hours are compared with the changes observed in control animals. The physiological variability of these animals has been analyzed statistically. The significance limits of the variability in the duration and the threshold of the after-discharge have been calculated according to

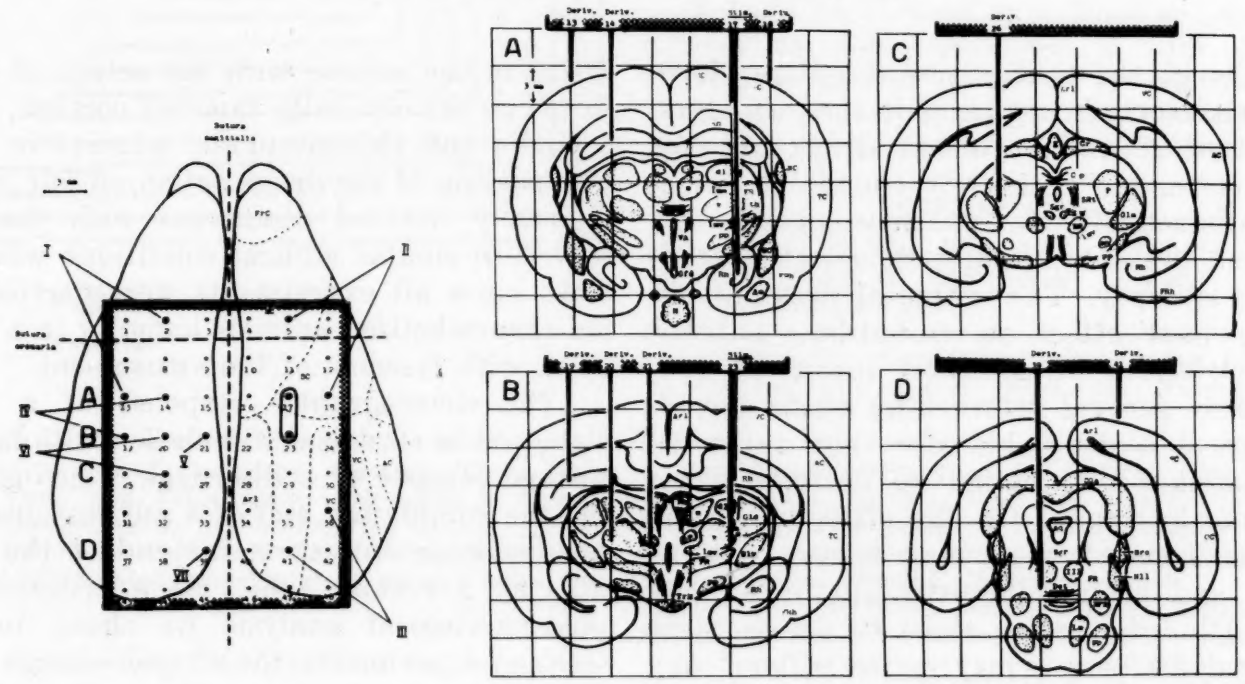


Fig. 1

Location of electrodes for cortical and subcortical stimulation and derivation. The stereotaxic coordinates are referred to the inferior edge of the socklet, when screwed on the skull.
AC = Auditory Cortex; Am = Nucl. amygdalae; Arl = Area limbica; Aq = Aquaed. Sylvii; Brc = Brach. conjunct.; Cfd = Col. forn. desc.; Cm = Corp. mamillaria; cm = centre médian thalami; Cr = Collic. rostr.; CQa = Corp. quadrig. ant.; Cp = Comissura post.; Dct = Decussatio tegm.; dl = Nucl. dors. lat. thalami; E = Epiphyse; EW = Nucl. Edinger-Westphal; FR = Form. reticul. (Midbrain); FRth = Form. reticul. thalami; Gld = Ggl. genic. dors.; Glm = Ggl. genic. med.; Glv = Ggl. genic. ventr.; H = Hypoph.; Hb = Nucl. habenulae; Lm = Lemn. med.; Imm = lam. medul. med.; lmv = lam. medul. ventr.; MC = Motor cortex; m = Nucl. dors. med. thalami; Nll = Nucl. lemn. lat.; NC = Nucl. caudatus; NFR = Nucl. form. reticul.; OC = Occipit. cortex; P = Putamen; pp = Pes pedunc.; Rh = Rhinencephalon; SC = Sensory cortex; Sgr = Subst. grisea centr.; sn = Subst. nigra; SRt = Subst. reticul. tegmenti; TC = Temporal cortex; VA = Tract. Vicq d'Azur; VC = Visual cortex; v = Nucl. ventr. thalami; III = Nucl. N. oculomot.

the formula: $d = t \cdot s \sqrt{\frac{N+5}{5N}}$, in which d = distance between the total average and one of the two significance limits, t = numerical constant, s = scatter of the control animals, N = total number of animals.[1]

RESULTS

A — Untreated control animals

In the first series of experiments, involving 10 unanesthetized, untreated rabbits, we determined the parameters to be used later for pharmacological analysis: the threshold in volts, the duration in seconds and the electrographic patterns of the electrically induced after-discharge. We considered furthermore the influence of the experimental conditions on those parameters, especially the influence of repeated stimuli, of increasing stimulus voltage, of the duration of the whole experiment (4½ hours), and finally, the role of brain lesions.

1. *The physiological parameters of cortical, diencephalic and rhinencephalic excitability.*

(*a*) The liminal voltage necessary to induce a self-sustained after-discharge, outlasting the end of the electrical stimulation, is the chief parameter in our experiments on the excitability of the stimulated structure. Its value represents the excitability threshold. This threshold is different in cortex, diencephalon and rhinencephalon. The average values established in 90 rabbits indicate the lowest threshold in the dorsal rhinencephalon (2.8 V.), whereas the threshold of the ventral rhinencephalon is definitely higher (6.0 V.). The highest threshold is found in the cortex (8.5 V.). The average threshold of the lateral thalamic structures (4.0 V.) is lower than the cortical, but higher than the dorsal rhinencephalic threshold. These values confirm the findings of other authors (Kaada 1951, Petsche and Monnier 1954).

(*b*) The duration of the after-discharge in seconds is another useful parameter, which also differs according to the stimulated structure. In 90 rabbits we found an average duration of 60 sec. for the cortical after-discharge, 85 sec. for the thalamus, 30 sec. for the dorsal rhinencephalon and 40 sec. for the ventral rhinencephalon.

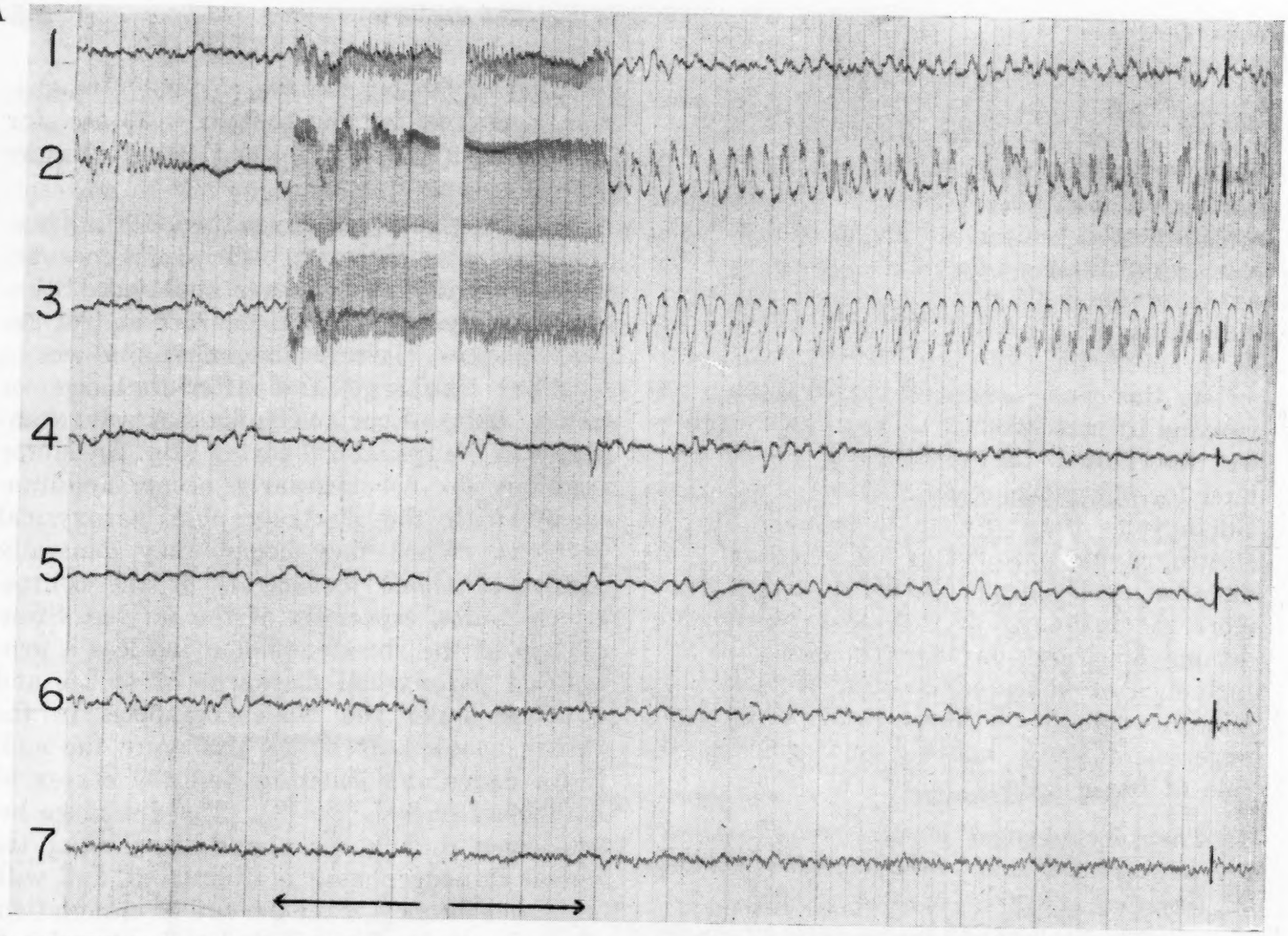
(*c*) The electrographic pattern of the after-discharge also shows a clear difference according to the structures stimulated. Stimulation of the sensorimotor cortex and of the diencephalon (lateral thalamus) induces a focalized discharge and after-discharge of spikes, sharp waves and spike and wave complexes in the ipsilateral cortex (fig. 2). Motor reactions do not regularly occur simultaneously with the electrographic paroxysmal patterns. When they occur, they generally consist of clonic movements of the contralateral limbs, especially of the foreleg. Stimulation of the rhinencephalon induces a generalised paroxysmal discharge of spikes and multiple spike and wave complexes in the rhinencephalon itself, the thalamus, the midbrain reticular formation and the cortex of both hemispheres (fig. 3). The discharge begins even during the stimulation, when the dorsal rhinencephalon is stimulated, and with a greater latency, after the end of stimulation, if the ventral rhinencephalon is stimulated. Motor reactions seldom occur. They occasionally consist of walking movements of the forelegs. The effect of the stimulus we use is definitely well circumscribed. This is proved by the fact that stimulation of the lateral thalamus, only 2 mm. from the highly excitable rhinencephalic structures, still induces a typical after-discharge in the ipsilateral thalamo-cortical system with lack of rhinencephalic components, even when stronger stimuli (15-20 V.) are used.

2. *The influence of experimental conditions on the parameters of excitability.*

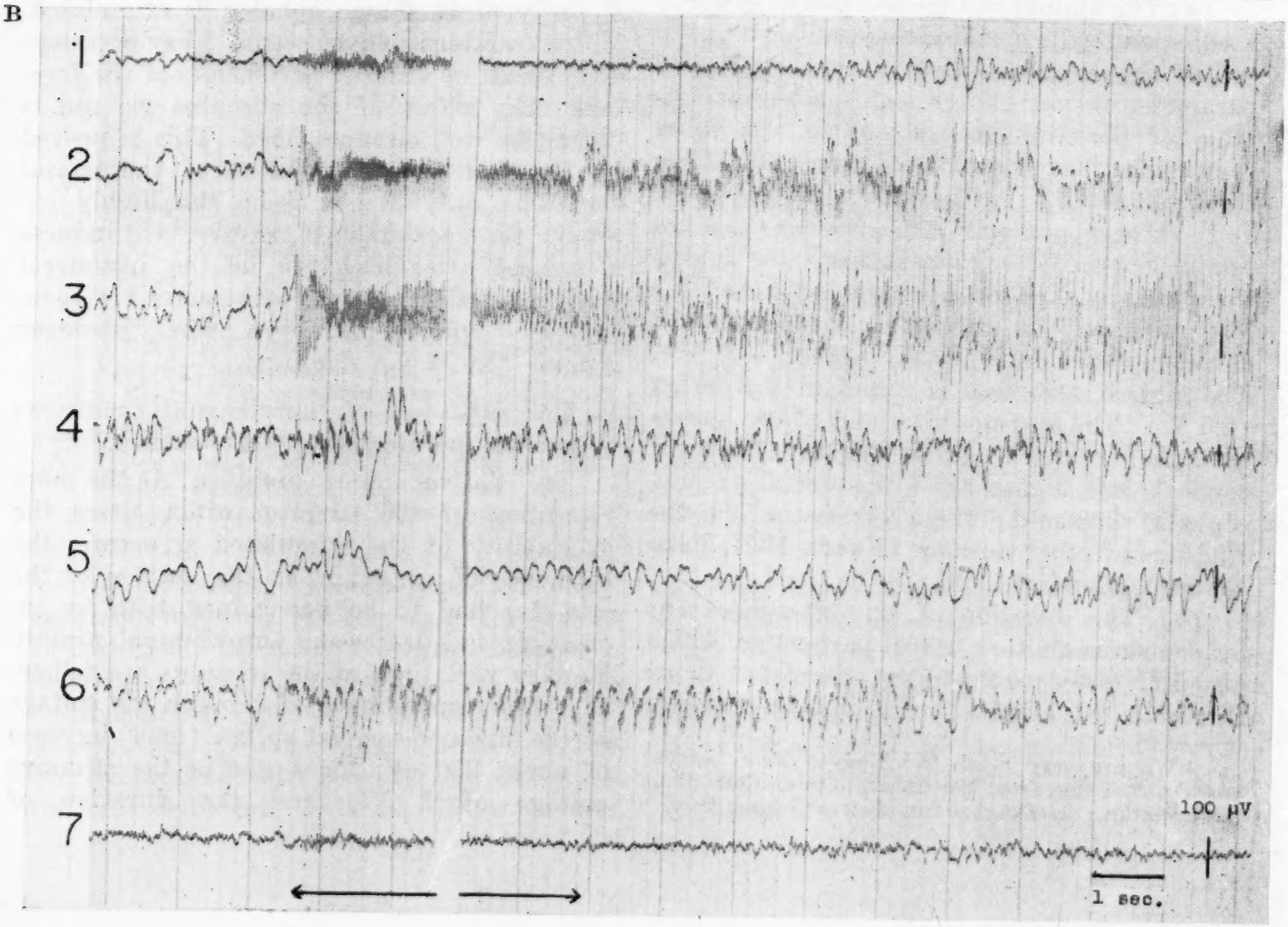
(*a*) *Voltage of the stimulus.* As the mere repetition of the stimulus often alters the excitability of the stimulated structure, the influence of variations in the voltage of the stimulus had to be determined both by increasing and decreasing supraliminal stimuli. Voltage variations of the stimulus are followed by corresponding variations in the voltage of the thalamo-cortical spikes (max. increase of about 250 μV. for a rise in the stimulus voltage of 2 V.) and the duration of

[1] We are very much indebted to Prof. Linder and Dr. A. Lang, from the Laboratoire de Statistique Mathématique in Geneva for their valuable help.

A



B



the thalamo-cortical after-discharge (max. lengthening of about 90 sec. for a rise of 2 V. in the stimulus voltage). The rhinencephalic after-discharge shows a tendency to shortening, both with increasing and decreasing voltages of the stimulus, whereas the voltage of the rhinencephalic spikes is more constant in similar conditions than the voltage of the thalamo-cortical spikes. Such effects can still be reproduced 1½, 3 and 4½ hours after the beginning of the experiment.

(*b*) *Repetition of the stimulation.* Repetition of the stimulation with the same voltage at regular intervals of 4 min. may increase the duration of the thalamo-cortical after-discharge up to 70 sec. and the voltage of the spikes up to 250 μV. after only 3 stimulations. In the rhinencephalon, on the contrary, repetition of the stimuli tends to shorten the after-discharge (down to 20 sec. after 3 repeated stimulations), whereas the voltage of the rhinencephalic spikes remains more steady than the voltage of the thalamo-cortical spikes.

(*c*) *Duration of the experiment.* Within 4½ hours after the beginning of the experiment, a slight increase of all thresholds is observed. In the cortex, the average maximal increase amounts to 0.95 V., in the thalamus to 1.1 V. and in the rhinencephalon to 0.9 V. (values established in 10 control animals). The cortical after-discharge may be lengthened (average maximum lengthening, 37 sec.). On the contrary a temporary shortening of the rhinencephalic after-discharge (max. 14 sec.) and of the diencephalic after-discharge (max. 18 sec.) may occur 1½ and 3 hours after the beginning of the experiment. Important alterations of the electrographic patterns were not observed within this time. A slight decrease of the voltage of the cortical spikes, a shortening of the wave component of the rhinencephalic multiple spike and wave complex, with a relative increase of the multiple spike discharges has been detected in some cases. The thalamic after-discharge pattern showed no significant alterations.

(*d*) *Brain lesions.* If the stimulated area was injured (haemorrhage, softening) a steep rise of threshold, up to 15 V. within one hour, and an occasional lengthening of the after-discharge 10 to 15 times the initial duration, were observed. It is possible that such changes were related to the necessity for increasing the stimulus voltage, since the excitability of the stimulated structure was decreased. Slow brain rhythms occurred occasionally. Most of the lesions were found in the electrically stimulated areas, but we cannot claim a systematic relation between the strength of the stimulus and the frequency of the lesions. The fact that in some cases stronger stimuli, up to 15 and 20 V., had to be used, had surprisingly little influence on the normal conditions of the experiment. Also, no close correlation was ever observed, within the range of the voltages used, between the incidence of brain lesions and the voltage of the stimulus, lesions occuring as often with low voltage stimuli.

B — Animals treated with anticonvulsant drugs

Every drug was administered orally and tested in 5 animals. The average values were established and compared with the results in control animals. The results of experiments followed by brain lesions were eliminated.

Fig. 2

Focalised cortical discharge and after-discharge of spikes and spike and waves induced in the ipsilateral (right) sensorimotor and occipital areas in the untreated rabbit by electrical stimulation of cortex and diencephalon.
A. Stimulation of cortex for 10 sec./4.4 V./1.0 msec.
B. Stimulation of lateral thalamus for 10 sec./35. V./1.0 msec.
1. L. sens. mot. cortex
2. R. sens. mot. cortex
3. R. occipit. cortex
4. L. rhinenc.
5. L. thalam. med.
6. L. thalam. lat.
7. Subst. retic. (midbrain)
Calibration 100 μV. Time-marker: 1 sec.

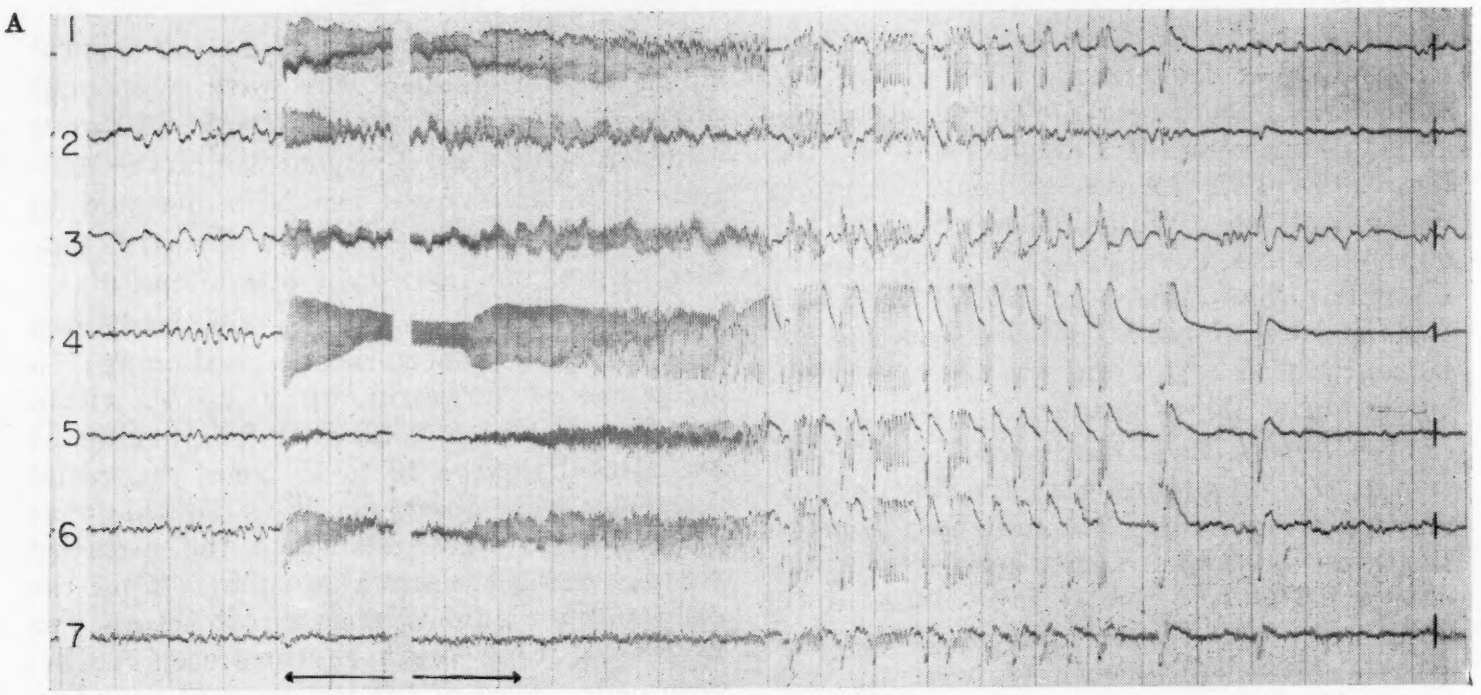


Fig. 3

Generalized multiple spikes and multiple spike and wave discharge and after-discharge induced in untreated rabbits by electrical stimulation of dorsal and ventral rhinencephalon. Note the longer latency after stimulation of the ventral rhinencephalon.

A. Stimulation of dorsal rhinencephalon for 10 sec./1.6 V./1.0 msec.

B. Stimulation of ventral rhinencephalon for 10 sec./5.0 V./1.0 sec.

1. L. sens. mot. cortex
2. R. sens. mot. cortex
3. R. occipit. cortex
4. L. rhinenc.
5. L. thalam. med.
6. L. thalam. lat.
7. Subst. retic. (midbrain)

Calibration: 100 μV. Time-marker: 1 sec.

1. *Hydantoin group.*

(*a*) *Diphenylhydantoin*: 100-150 mg/kg. This drug has a marked action on the diencephalon (fig. 4A). It clearly rises the thalamic threshold from 3 to 12 V. and shortens the diencephalic afterdischarge from 90 to 30 sec. within 4½ hours. Electrographically, it slows down the sharp waves and the wave components of the spike and wave complexes induced in the cortex by diencephalic stimulation. It also increases the production of slow waves induced by stimulation of the thalamus (fig. 5). On the contrary it does not alter the pattern of the afterdischarge induced by stimulation of the cortex or of the rhinencephalon. The thresholds of these structures are not modified, whereas the duration of the rhinencephalic after-discharge is increased.

(*b*) *Methyl-dibrom-phenyl-ethyl-hydantoin* (*Anirrit*): 800-1000 mg/kg.

This derivative of hydantoin has an influence on the thalamo-cortical system, which is slightly stronger at the cortical than at the diencephalic level. It clearly rises the cortical and the thalamic thresholds from 2.5 to 12 V. within 4½ hours. Furthermore, it shortens the cortical after-discharge from 70 to 30 sec. within 3 hours, but does not alter the duration of the after-discharge induced by thalamic stimulation. Electrographically, it reduces the spikes and the sharp waves inducted by cortical or by diencephalic stimulation (fig. 5). Finally it seems to increase slightly the excitability of the rhinencephalon; although it has no influence on its threshold, it lengthens markedly its after-discharge, and increases the rate and voltage of the spikes and multiple spikes more than in the control animals.

2 *Phenylacetylurea* (*Phenurone*): 100-200 mg/kg.

This drug has an action on the diencephalo-cortical system. It rises the threshold of the cortex from 3 to 14 V. and of the diencephalon from 2.5 to 9 V. within 4½ hours, and shortens the diencephalic afterdischarge from 100 to 20 sec. within the same time (fig. 4B). Electrographically, it abolishes the cortical spikes induced by stimulation of the thalamus and substitutes sharp waves (fig. 6). Although it does not show a significant influence on the threshold of the rhinencephalon, it does reduce the amount of the spikes and multiple spikes evoked by rhinencephalic stimulation and lowers their voltage. At the same time, it enhances the wave components of the rhinencephalic response, mainly in the dorsal rhinencephalon and in the cortex (fig. 6).

3. *Trimethadione* (*Tridione*): 1500-2000 mg/kg.

The drug acts on the three investigated structures if a sufficient dose is administered (fig. 4C). It elicits a marked increase of the cortical threshold from 5 to 14 V. within 4½ hours and shortens the after-discharge induced by cortical stimulation from 30 to 10 sec. within 1½ hours. It diminishes slightly the sharpness of the sharp waves, but does not alter the spikes in the cortical after-discharge. It rises the diencephalic threshold from 4.5 to 12 V. within 4½ hours, but does not shorten the after-discharge conspicuously and does not modify the pattern of the diencephalic after-discharge. Finally it increases slightly the rhinencephalic threshold from 4 to 8 V. within 4½ hours and lengthens somewhat the rhinencephalic after-discharge, without modifying definitely its pattern. The silent periods between the rhinencephalic multiple spikes show an occasional tendency to disappear and the multiple spikes are sometimes replaced by continuous spike paroxysms.

4. *Phenobarbital* (*Luminal*): 30-60 mg/kg.

This drug has a definite action on the diencephalic after-discharge and a somewhat slighter influence on the rhinencephalon. It rises markedly the threshold from 3 to 14 V. within 4½ hours and shortens the after-discharge induced by diencephalic stimulation from 90 to 30 sec. within 1½ hours. It also rises the rhinencephalic threshold from 3 to 10 V. within 3 hours. The excitability of the cortex is *increased* and its threshold lowered from 17 to 13.5 V. within 3 hours (fig. 4D). The pattern of the after-discharge remains undisturbed.

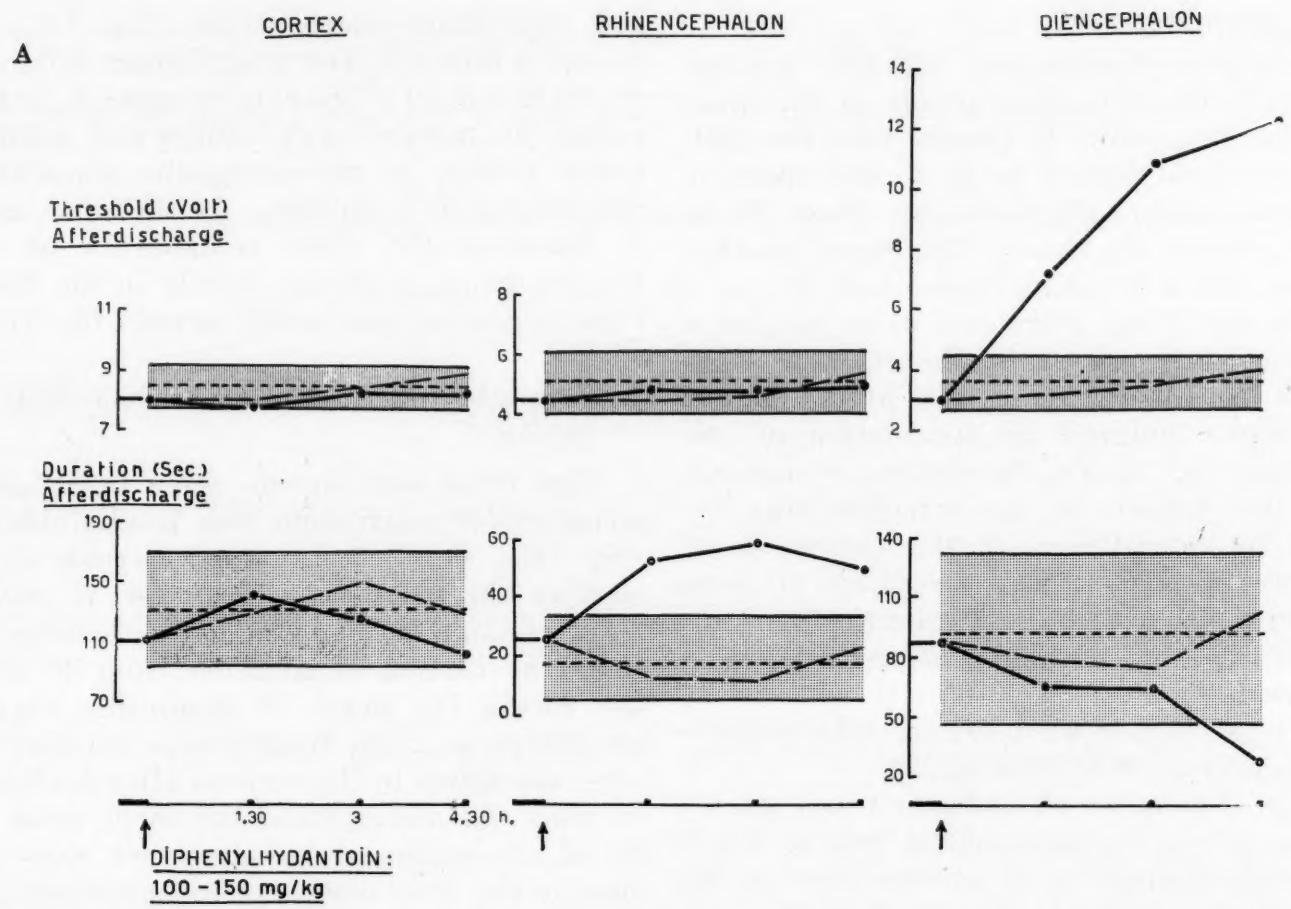
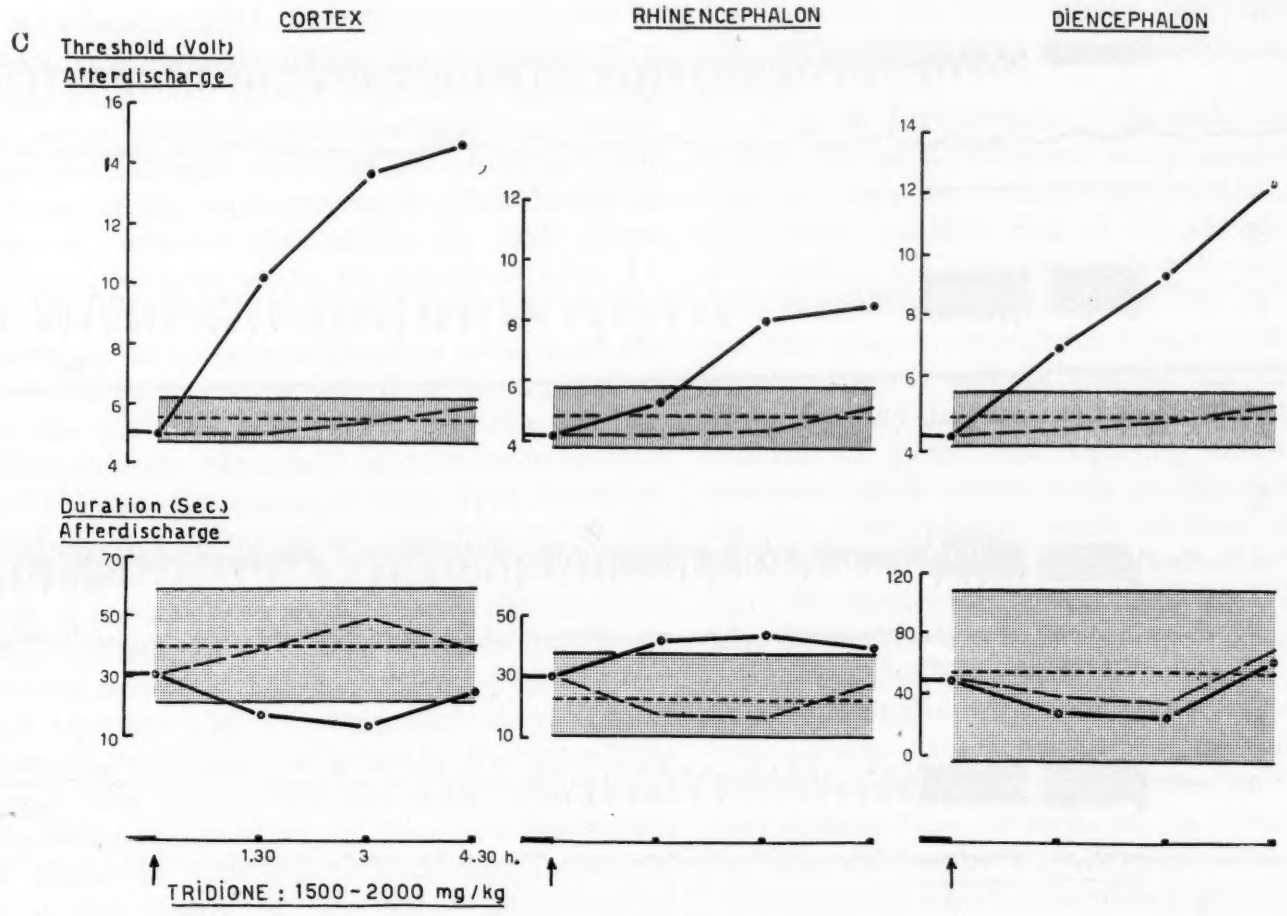


Fig. 4

Influence of diphenylhydantoin (A) and Phenurone (B) on threshold and duration of cortical, rhinencephalic and diencephalic after-discharge.



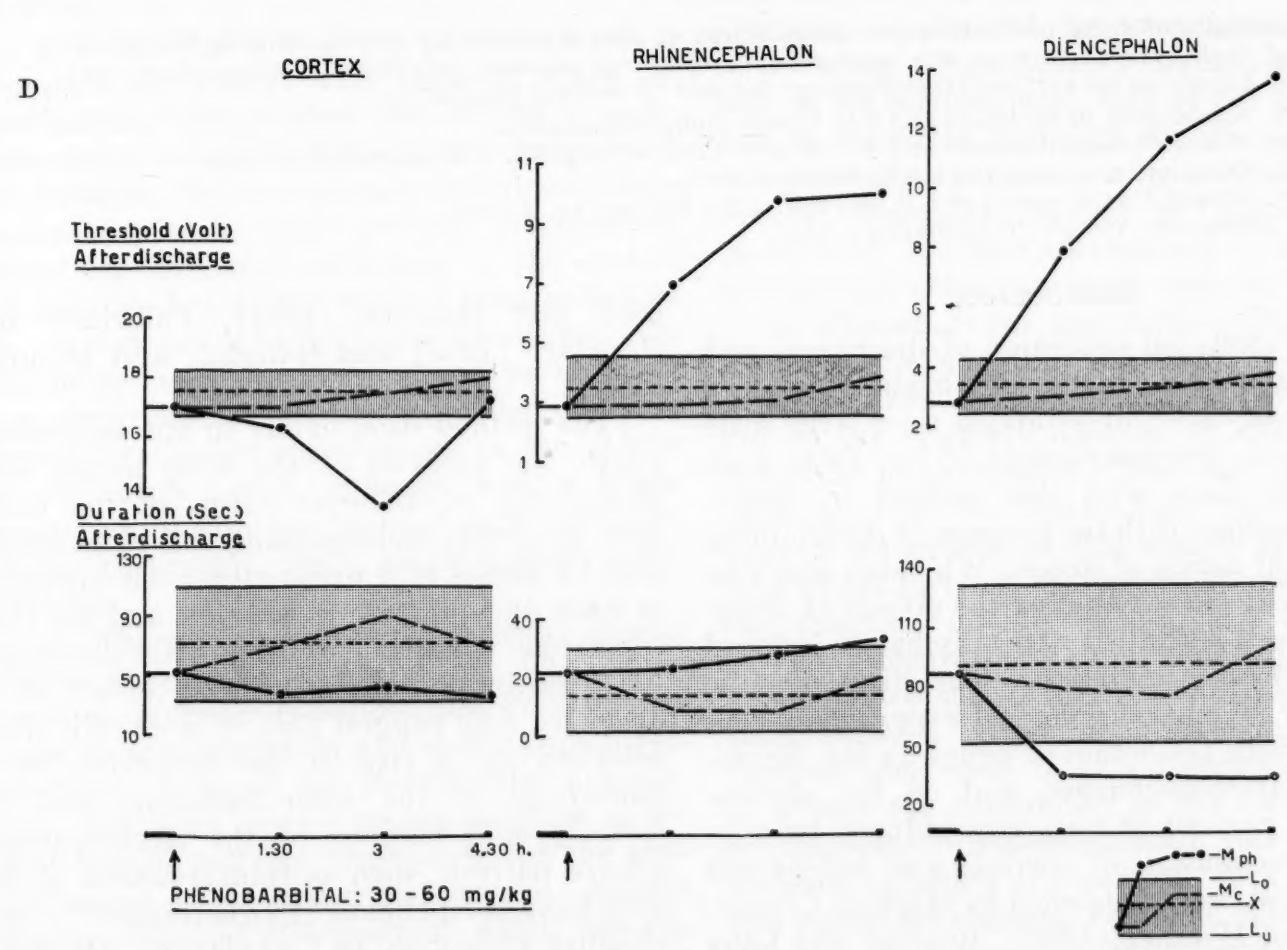


Fig. 4 (Cont.)

Influence of Tridione (C) and Phenobarbital (D) on threshold and duration of cortical, diencephalic and rhinencephalic after-discharge (Average values).
M_c = Untreated control animals; M_{ph} = Treated animals; L_o and L_u = Significance limits.

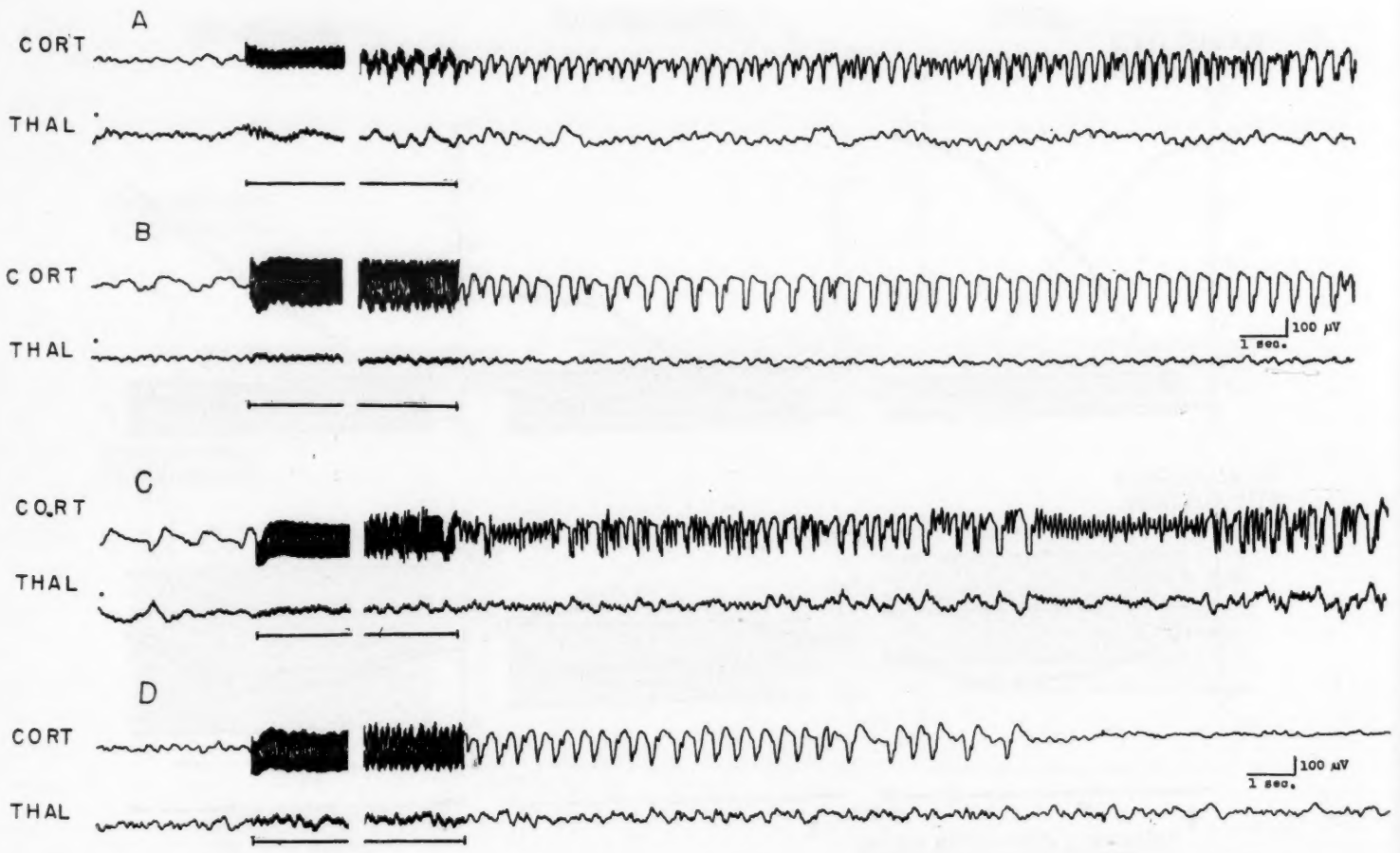


Fig. 5

Decrease of spike production and enhancement of slow waves in the cortex, showing the action of diphenylhydantoin on the cortical after-discharge induced by thalamic stimulation, and of Anirrit on the cortical after-discharge induced by cortical stimulation.

A. Stimulation of thalamus at 1.5 V. before diphenylhydantoin.
B. Stimulation of thalamus at 2 V. one hour after 100 mg/kg. of diphenylhydantoin.
C. Stimulation of cortex at 1.5 V. before Anirrit.
D. Stimulation of cortex at 2 V. one hour after 800 mg/kg. Anirrit.
Calibration: 100 μV. Time-marker: 1 sec.

DISCUSSION

The electrical induction of discharges and after-discharges in definite brain structures has already been investigated on a large scale by various neurophysiologists, but little work has been done with this method in neuropharmacology with the purpose of determining the site of action of drugs. Whieldon and Van Harreveld (1951) studied the effects of drugs on the self-sustained after-discharge induced by cortical stimulation. The first results, however, of pharmacological experiments concerned with the action of drugs on the threshold of after-discharges, and on the electrographic pattern of responses induced by electrical stimulation of cortical and subcortical structures, were published by Herken, Cooper, Laue and Monnier (1952), Monnier and Laue (1953), Schuetz and Caspers (1954), Gangloff and Monnier (1954), Falbriard and Gangloff (1955) and Gangloff and Monnier (1955).

The method used to-day in our laboratory allows the analysis of the drug action simultaneously at different levels of the brain such as cortex, diencephalon, and rhinencephalon by means of 3 parameters: the threshold in volts, the duration in seconds, and the electrographic pattern, of the after-discharge. As regards the anticonvulsant effect of a drug, we may suggest that it is chiefly characterized by a rise in the threshold, by a shortening of the after-discharge, and by definite modifications of the electrographic seizure pattern, such as reinforcement of the slow-wave components (''Bremswellen'') and of other refractory or ''phylactic'' (Walter) processes (see also Monnier and Laue 1953).

It may happen that these three parameters be modified separately under the influence of a drug, since they do not represent necessarily the same physiological mechanism. Phenurone, for example, modifies the electrographic pattern of the rhinencephalic after-discharge (fig. 6) without shortening its total duration and without rising its threshold (fig. 4). Phenobarbital and Tridione have no marked influence on the electrographic pattern of the after-discharge, in spite of a strong action on the threshold (fig. 4). A rise of the rhinencephalic threshold after administration of Tridione, for example, may even be correlated with a paradoxical lengthening of the after-discharge (fig. 4), possibly due to the lack of mechanisms antagonizing the multiple spike discharges. Finally, the lowering of the cortical threshold, already observed by Schuetz and Caspers (1954) after administration of phenobarbital and confirmed by our investigations, does not necessarily occur with a simultaneous lengthening of the after-discharge, as might be expected if both manifestations were the result of the same physiological activity.

It is not the aim of the present paper to compare our results with those of other investigators, who studied the effects of anticonvulsant drugs in Metrazol or electroshock convulsions. We have already stated that these methods provide only general information, about the efficiency of a drug in the control of seizures, but do not allow determination of its impact on definite brain structures. On the other hand we are inclined to correlate our experimental results with the data afforded by clinical observations on the effects of the drugs tested, although such a transposition to the human brain of facts established for the rabbits brain needs critical interpretation.

1. There is no doubt, that drugs having a protective action on grand mal, like phenobarbital, diphenylhydantoin and even Phenurone, rise the threshold and shorten the after-discharge induced by diencephalic stimulation. This may mean a strong decrease of the diencephalic activity responsible for the generalization of the grand mal seizure. Anirrit also, the clinical efficiency of which was demonstrated in cases of grand mal (Janz 1953), rises the diencephalic threshold without shortening the diencephalic after-discharge.

2. It is furthermore noticeable that Tridione, the most efficient drug against petit mal, develops its strongest activity at the cortical level: marked rise of the threshold and shortening of the cortical after-discharge. This suggests that the excitability of the cortex may play as important a role in the mechanism of petit mal as that of the diencephalon. It may be assumed therefore that the control of petit mal epilepsy requires an anticonvulsant action both on the cortex and on the diencephalon, such as that provided by Tridione. On the other hand it is possible that the strong protective action of Tridione may be partly due to its action on the rhinencephalon, characterized by a slight increase of the after-discharge threshold. These facts may in any case account for the smaller effectiveness of diphenylhydantoin on the petit mal seizure type, in spite of its strong action on the diencephalon. Anirrit, the clinical efficiency of which was also reported in certain cases of petit mal (Janz 1953), is — with Tridione — alone of the investigated drugs, in inducing a significant combined modification at the cortical level, both of the threshold and of the after-discharge duration. It may be significant that the smaller increase of the cortical threshold induced by Anirrit compared with Tridione corresponds to a weaker therapeutic effect on petit mal in humans.

3. Phenobarbital and diphenylhydantoin, known for a long time as the most efficient drugs against cortical focal epilepsy, do not induce the slightest increase of the cortical threshold in the rabbit. This may prove the importance of the diencephalic hyperexcitability in the genesis of this seizure type, since both drugs increase the threshold and shorten the duration of the diencephalic after-discharge. Regarding Tridione and petit mal epilepsy, we stated above, that the correlations between cortex and thalamus are so intricate that even in this diencephalic type of seizure the excitability of the cortex plays an important, underestimated role. In the reversed situation of a cortical, focal epilepsy this statement remains valuable. The cortico-diencephalic interactions are so important that

we are prone to admit that even the genesis of the cortical jacksonian seizure involves a diencephalic hyperactivity. In this regard one of us has repeatedly emphasized the fact that jacksonian epilepsy, which was always considered as the result of a purely cortical focal excitation, may also have a diencephalic origin. It was shown that electrical stimulation of the ventro-lateral thalamus in man may induce a contralateral jacksonian seizure, with bilateral wave and spike discharge of diencephalic epileptic type, but predominant on the stimulated side (Monnier 1949; Monnier and Fischer 1950; Monnier 1951 and 1953; Monnier quoted by Gastaut 1954). It was suggested that such "diencephalic jacksonian seizures" may occur when the ventro-lateral thalamus fires the ipsilateral cortical motor area (Monnier 1953, 1955). Furthermore there has been demonstrated in the rabbit the existence of a similar diencephalic pseudo-jacksonian seizure type, induced by stimulation of the lateral thalamus, with movements of the contralateral legs (Monnier and Laue 1953). Numerous later experiments (Petsche and Monnier 1954; Gangloff and Monnier 1955) have confirmed this observation. It is therefore understandable why phenobarbital and diphenylhydantoin, with their marked action on the diencephalon (increase of threshold and shortening of duration of the diencephalic after-discharge) are efficient in cortical epilepsy, in spite of their lack of cortical action. The efficiency of phenobarbital in this type of seizure may in addition be due to its action on the rhinencephalon (rise in threshold of the rhinencephalic after-discharge).

4. That Phenurone is especially active in temporal epilepsy (psychomotor seizures) may partly be explained by its action on the cortex and on the diencephalon, preventing the generalization of temporal focal excitation. That Phenurone does not modify the rhinencephalic threshold seems at first surprising, since it is active in temporal lobe epilepsy. The analysis of the electrographic pattern of the rhinencephalic after-discharge (fig. 6) however, shows definite changes: reduction in voltage and frequency of the multiple spikes, with reinforcement of the wave components. These changes in the after-discharge pattern already mentioned by Monnier and Laue (1953) may explain the more specific anticonvulsant action of the drug in psychomotor epilepsy.

The case of Phenurone proves once more that a drug may modify one parameter alone — in this case the electrographic pattern of the rhinencephalic after-discharge — without affecting other parameters. This specific pattern alteration leads us to discuss the mechanisms involved in the after-discharge pattern. It is not possible, of course, to take into account here all the theories concerning this problem. On the basis of our own observations we may, however, point out the following facts:

It has often been suggested that the epileptic discharge may involve two antagonistic central mechanisms, a spike producing system and a system producing slow waves. Against this too schematic conception, our experiments show that spikes or sharp waves can be induced in any of the structures we stimulated, in the diencephalon, in the cortex itself, and especially in the rhinencephalon. For this reason we must conclude that the spike is the usual response of every brain and nerve tissue to an effective stimulus. However, it is possible that the massive spikes and sharp wave discharges and after-discharges induced by electrical stimulation of the rabbit's brain may be due to facilitatory and summative, mechanisms involving the cooperation of many systems, for example the reticular system, the rhinencephalon, and so on.

On the other hand nothing allows us to ascribe the slow wave components to one specific system. We admit that they are the result of a "phylactic" mechanism (Grey Walter 1938, 1953) or of a "Brems" mechanism (Jung 1941). In fact, they may be evoked even in isolated brain tissue after local stimulation. They do not involve necessarily the correlative action of specific brain systems. The slow wave component which follows a spike or a sharp wave may be an elementary unspecific, protective reaction of the brain tissue to any stronger stimulus. Here also it is possible however that such elementary protective reactions may be enhanced by some more definite brain structures. Gastaut (1955) considered the thalamo-cau-

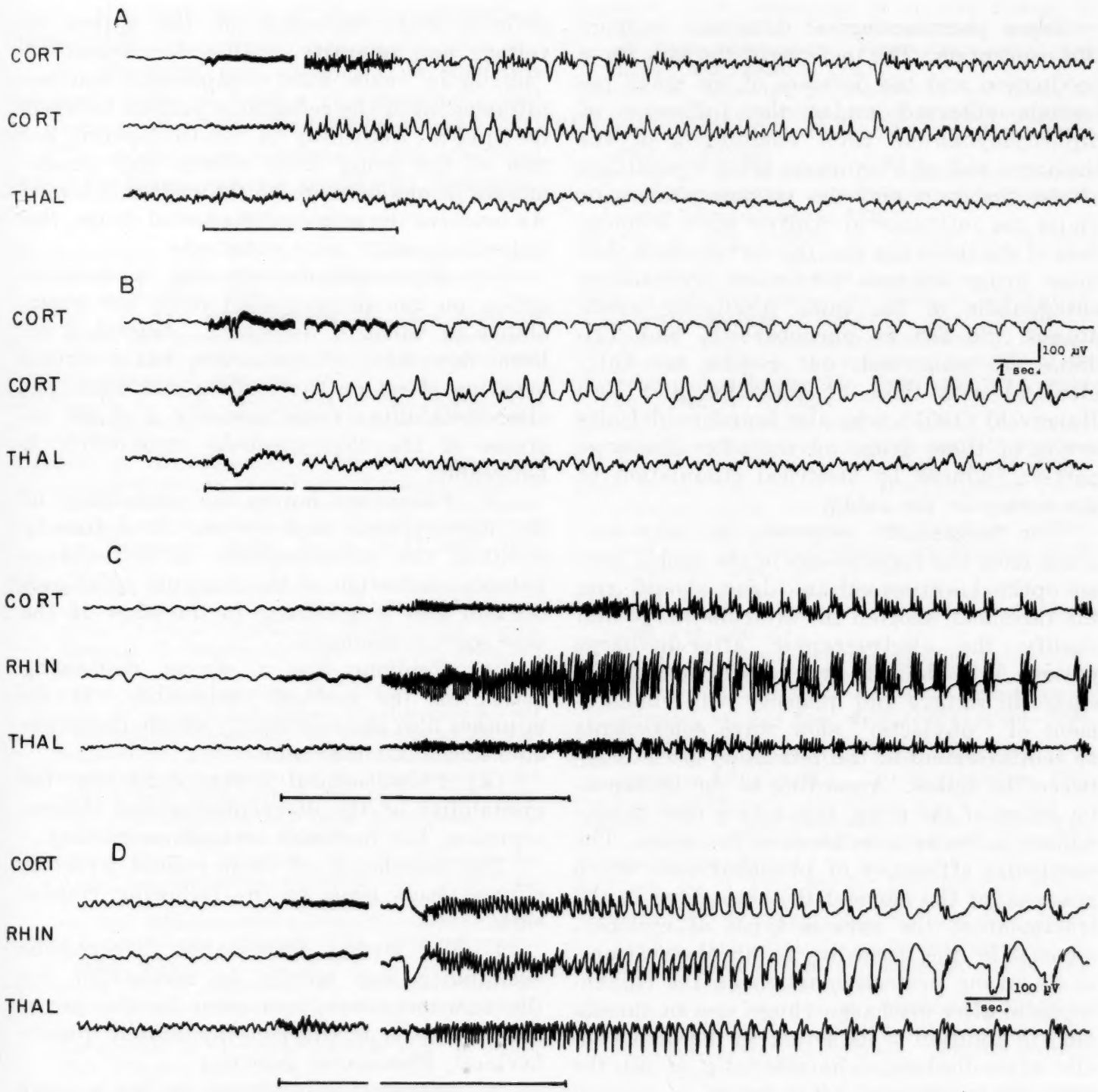


Fig. 6

Inhibition of the spike components and enhancement of the slow waves in the cortex after diencephalic stimulation and in both the cortical and subcortical areas, more especially in the rhinencephalon, after rhinencephalic stimulation, showing the influence of Phenurone on the electrographic after-discharge pattern.
A. Stimulation of thalamus at 1 V. before Phenurone.
B. Stimulation of thalamus at 3 V. one hour after 150 mg/kg. Phenurone.
C. Stimulation of rhinencephalon at 1 V. before Phenurone.
D. Stimulation of rhinencephalon at 1 V. one hour after 150 mg/kg. Phenurone.
Calibration: 100 μV. Time-marker: 1 sec.

date structures as such a slow wave producing system. Some as yet unpublished data, from experiments we performed more recently in the rabbits brain, suggest that some medial thalamic structures, with their more pronounced property of recruiting slow wave components, could have some phylactic, protective functions.

Some pharmacological data also support this conception. The increase of the slow wave production and the decrease of the spike potentials observed under the influence of diphenylhydantoin after stimulation of the thalamus and of Phenurone after stimulation of the thalamus and the rhinencephalon, or under the influence of Anirrit after stimulation of the thalamus and the cortex, show that these drugs enhance protective mechanisms antagonistic to the spike producing mechanisms. So far as phenobarbital and Tridione are concerned, our results are fully identical with those of Whieldon and Van Harreveld (1951), who also found no definite action of these drugs on the after-discharge pattern induced by electrical stimulation of the cortex in the rabbit.

For therapeutic purposes, we may conclude from our experiments in the rabbit, that an optimal anticonvulsant drug should rise the threshold, shorten the after-discharge and modify the electrographic after-discharge pattern in a definite way: reduction of the spikes in voltage and quantity with enhancement of "phylactic" slow wave components or reinforcement of the refractory periods between the spikes. According to the therapeutic effect of the drug, this action may predominate in one or more levels of the brain. The particular efficiency of phenobarbital, which remains for the moment the basic drug in the treatment of the various types of epilepsy, seems to be due, according to our observations, to its strong protective action on the rhinencephalic after-discharge (huge rise in threshold) in addition to its action on the diencephalic after-discharge characteristic of all the other anticonvulsant drugs tested.

SUMMARY

The local action of some clinically familiar anticonvulsant drugs on the brain of the unanesthetized rabbit has been investigated by electrical stimulation of the cortex, diencephalon and rhinencephalon. The pharmacological action has been analyzed with 3 parameters: the threshold, the duration and the pattern of the electrically induced after-discharge. This action may rise the threshold, shorten the duration and modify the electrographic pattern of the after-discharge in a definite way: reduction of the spikes in voltage and quantity, with enhancement of "phylactic" slow wave components and reinforcement of the refractory periods between the spikes. According to the therapeutic action of the drug, these effects may predominate in one or more of the explored levels. As concerns the action of the tested drugs, the following results were obtained:

(*a*) *Diphenylhydantoin* has a definite action on the diencephalon only, the excitability of which is decreased. *Anirrit,* a dibrom derivative of hydantoin, has a strong lowering effect on the cortical and diencephalic excitability; simultaneously a slight increase of the rhinencephalic excitability is noticeable.

(*b*) *Phenurone* lowers the excitability of the diencephalon and cortex. It definitely modifies the rhinencephalic after-discharge pattern: reduction of the multiple spike production and lengthening in duration of the slow wave components.

(*c*) Tridione has a strong depressing action on the cortical excitability. It diminishes also the excitability of the diencephalon and rhinencephalon.

(*d*) *Phenobarbital* lowers definitely the excitability of the diencephalon and rhinencephalon, but increases cortical excitability.

The correlation of these results with the clinical facts leads to the following conclusions:

1. The strong decrease in diencephalic excitability may chiefly be responsible for the anticonvulsant protection in the *grand mal* seizure type (diphenylhydantoin, phenobarbital, Phenurone, Anirrit).

2. Anticonvulsant drugs having a more definite action on the *petit mal* seizure (Tridione, Anirrit) decrease both the diencephalic and cortical excitability. This suggests that not only diencephalic but also cortical mechanisms are involved in the petit mal seizure.

3. The fact that *cortical focal epilepsy* requires mainly a strong diencephalic protection (phenobarbital, diphenylhydantoin) suggests on the other hand that even cortical jacksonian epilepsy may depend on diencephalic hyperexcitability. This and the so called "diencephalic jacksonian seizure" first described by Monnier (1949, 1951, 1953)

prove the importance of diencephalocortical interaction.

4. *Temporal lobe epilepsy* (psychomotor seizure) needs at least a rhinencephalic and a diencephalic protection (Phenurone).

The mechanisms involved in the electrical after-discharge pattern are briefly discussed.

REFERENCES

ALAJOUANINE, TH. *Les grandes activités du lobe temporal; Actualités neuro-physiologiques.* Masson et Cie Edit., **1955.**

BARANY, E. and STEIN-JENSEN, E. The mode of action of anticonvulsant drugs on electrically induced convulsions in the rabbit. *Arch. int. Pharmacodyn.*, **1946**, *73*: 1-47.

BURNS, D. B. The mechanisms of the epileptiform afterdischarge. *EEG Clin. Neurophysiol.*, **1953**, *5*: 464.

CASPERS, H. Tierexperimentelle Untersuchungen über die Provokation kortikaler Krampfstromherde durch Narkotika und Hypnotika und die Beziehung der Fokusaktivität zur Krampferregbarkeit der Hirnrinde. *Zschr. Exper. Med.*, **1953**, *122*: 142.

EVERETT, G. M. and RICHARDS, R. K. Comparative anticonvulsant action of 3,5,5-Trimethyloxazolidine-2,4-Dione (Tridione), Dilantin and Phenobarbital. *J. Pharmacol. Exper. Therap.*, **1944**, *81*: 402-407.

FALBRIARD, A. et GANGLOFF, H. Action d'un inhibiteur de la carboanhydrase, l'acétazolamide, sur l'excitabilité du cortex, du thalamus et du rhinencéphale. *Experientia*, **1955**, *11*: 234-237.

GANGLOFF, H. und MONNIER, M. Bestimmung der elektrischen Erregbarkeit von Cortex, Diencephalon und Rhinencephalon beim Kaninchen. *Pflügers Arch.*, **1955**, *261*: 421-433.

GANGLOFF, H. und MONNIER, M. Bestimmung des Angriffsmechanismus antikonvulsiver Pharmaka durch elektrische Reizung von Cortex, Diencephalon und Rhinencephalon beim Kaninchen. *Acta Neurochirurgica* (Suppl. III) **1955**, Springer Verlag, Wien.

GANGLOFF, H. et MONNIER, M. Détermination du mode d'action des principales substances anticonvulsivantes par stimulation du cortex, du diencéphale et du rhinencéphale chez le lapin. *Helv. Physiol. Acta*, **1955**, *13*: C15-C17.

GANGLOFF, H. et MONNIER, M. Démonstration de l'impact des analgésiques morphiniques et d'une substance antimorphinique sur le cortex et le subcortex du lapin (thalamus, rhinencéphale et substance réticulée), *Helv. Physiol. Acta*, **1955**, *13*: C47-C49.

GASTAUT, H. *The epilepsies*, Charles C. Thomas Edit., **1954.**

GASTAUT, H. Physiopathogénie des épilepsies. *Méd. gén. fran.*, **1955**, *4*: 259-262.

GIBBS, F. A., EVERETT, G. M. and RICHARDS, R. K. Phenurone in Epilepsy, presented before the Amer. Br. Internat. League against Epilepsy, June **1948.**

GOODMAN, L. S., TOMAN, J. E. P. and SWINYARD, E. A. The anticonvulsant properties of Tridione: laboratory and clinical investigations. *Amer. J. Med.*, **1946**, *1*: 213-228.

GOODMAN, L. S., SWINYARD, E. A. and TOMAN, J. E. P. Studies on the anticonvulsant properties of diphenylhydantoin. *Proc. Fed. Amer. Soc. Exper. Biol.*, **1946**, *5*: 180.

HERKEN, H., MONNIER, M., COOPER, H. und LAUE, H. Hemmung subkortikal ausgelöster Krampfpotentiale durch Hexachlorcyclohexan. *Experientia*, **1952**, *8*: 432-434.

HESS, W. R. *Die Methodik der lokalisierten Reizung und Ausschaltung subkortikaler Hirnabschnitte.* Georg Thieme, Leipzig, **1932.**

HUNTER, J. and JASPER, H. Effects of thalamic stimulation in unanesthetized animals. *EEG Clin. Neurophysiol.*, **1949**, *3*: 305-324.

JANZ, D. Die Behandlung der Epilepsie mit Anirrit. *Nervenarzt*, **1953**, *5*: 208-213.

JASPER, H. and DROOGLEEVER-FORTUYN, J. Experimental studies on the functional anatomy of the petit mal epilepsy. *Res. Publ. Ass. nerv. ment. Dis.*, **1946**, *26*: 272-298.

JASPER, H., HUNTER, J. and KNIGHTON, R. Experimental studies of thalamo-cortical systems. *Trans. Amer. Neur. Assoc.*, **1948**, *73*: 210-212.

JUNG, R. und TÖNNIES, F. J. Hirnelektrische Untersuchungen über die Entstehung und Erhaltung von Krampfentladungen. Die Vorgänge am Reizort und die Bremsfähigkeit des Gehirns. *Arch. Psychiatr.*, **1941**, *185*: 701-735.

JUNG, R. Hirnelektrische Untersuchungen über den Elektrokrampf. *Arch. f. Psychiatr. u. Z. Neur.*, **1949**, *183*: 206-244.

KAADA, B. R. Somato-motor, autonomic and electrocorticographic responses to electrical stimulation of rhinencephalic and other structures in primates, cat and dog. *Acta physiol scand.*, **1951**, 23, Suppl. 83.

LAUE, H. Le mode d'action anticonvulsivante d'un dérivé de l'Hydantoïne. *Therap. Umschau*, **1955**, *10*: 177-179.

LIBERSON, W. T. and CADILHAC, J. Les crises hippocampiques expérimentales. *Montpellier médical*, **1954**, *6*: 515-547.

MONNIER, M. et FISCHER, R. Contributions expérimentales à la physiologie du tronc cérébral chez l'homme. II. Stimulation et coagulation des noyaux latéro-ventral, ventro-postéro-latéral et ventro-postéro-médian du thalamus. *Helv. Physiol. Acta*, **1950**, *8*: C55-C57.

MONNIER, M. et FISCHER, R. Stimulation électrique et coagulation thérapeutique du thalamus chez l'homme (névralgies faciales). *Confinia Neurol.*, **1951**, Separ. 11, Fasc. *5*: 282-286.

MONNIER, M. et LAUE, H. Technique de dérivation des activités électriques corticales et sous-corticales pendant la stimulation du diencéphale chez le lapin. *Helv. Physiol. Acta*, **1953**, *11*: 73-80.

MONNIER, M. et LAUE, H. Action de diverses substances sédatives et anticonvulsivantes sur les crises d'épilepsie provoquées par stimulation du rhino-diencéphale chez le lapin. *Helv. Physiol. Acta*, **1953**, *11*: C70-C72.

MONNIER, M. et LAUE, H. Epilepsie diencéphalique par stimulation du système intralaminaire thalamique chez le lapin. *Helv. Physiol. Acta*, **1953**, *11*: C23-C25.

MONNIER, M. Repérage, stimulation et coagulation thérapeutique des centres sous-corticaux chez le singe et chez l'homme. *IVe Congr. Neurol. Intern.*, **1949**, *C. R.*, **1951**, *3*: 188-191.

MONNIER, M. Le rôle du thalamus dans l'organisation de la douleur. *Acta Neuroveget.*, **1953**, *7*: 84-92.

MONNIER, M. La stimulation électrique du thalamus chez l'homme. *Rev. Neurol.*, **1955**, *93*: 267-277.

MORUZZI, G. *L'epilessia sperimentale.* Zanichelli Edit., Bologna **1946**.

PENFIELD, W. Posttraumatic epilepsy. *Amer. J. Psychiat.*, **1944**, *100*: 750-761.

PETSCHE, M. und MONNIER, M. Die elektrische Aktivität der Hirnrinde und des Zwischenhirns bei Reizung von Cortex, Rhinencephalon und Diencephalon. *Helv. Physiol. Acta*, **1954**, *12*: 123-136.

PETSCHE, H., MARKO, A. und MONNIER, M. Mikrozeitliche, toposkopische Analyse bioelektrischer Hirnwellen beim Kaninchen. *Helv. Physiol. Acta*, **1955**, *13*: 354-371.

SCHÜTZ, E. and CASPERS, H. On the provocation and activation of epileptic discharges by anesthesia and sleep induced by medicaments. *EEG Clin. Neurophysiol.*, **1953**, *5*: 118.

SCHÜTZ, E. und CASPERS, H. Ueber die bioelektrische Hirnrindenaktivität und ihre Steuerung durch Stammhirnstrukturen. *Z. f. d. ges. Innere Med. und ihre Grenzgeb.*, **1954**, *19/20*: 1037-1056.

SWINYARD, E. A. Validity of laboratory anticonvulsant tests for predicting antiepileptic potency and specificity. *Proc. Fed. Amer. Soc. Exp. Biol.*, **1947**, *6*: 376.

TOMAN, J. E. P. The neuropharmacology of antiepileptics. *EEG Clin. Neurophysiol.*, **1949**, *1*: 33-44.

TOMAN, J. E. P., EVERETT, G. M. and RICHARDS, R. K. Search for new drugs against epilepsy. *Texas Rep. Biol. Med.*, **1952**, *10*: 96-104.

TOMAN, J. E. P. and TAYLOR, J. D. Mechanism of action and metabolism of anticonvulsants. *Epilepsia*, **1952**, *1*: 31-48.

VERDEAUX, G. et MARTY, R. Action sur l'électroencéphalogramme de substances pharmacodynamiques d'intérêt clinique. *Rev. Neurol.*, **1954**, *6*: 428-444.

WALKER, A. E. *Posttraumatic epilepsy.* Charles C. Thomas Publ., Springfield, **1949**.

WALTER, W. GREY. *The living brain.* Gerald Duckworth, London, **1953**, p. 170.

WHIELDON, J. A. and VAN HARREVELD, A. Drug effects in the results of minimal cortical stimulation. *EEG Clin. Neurophysiol.*, **1951**, *1*: 31-35.

WINKEL, K. und CASPERS, H. Untersuchungen an Reptilien über die Beeinflussung der Grosshirnrindenrhythmik durch Zwischenhirnreizungen mit besonderer Berücksichtigung des Thalamus. *Pflügers Arch. Physiol.*, **1953**, *258*: 22-37.

WYSS, O. A. M. Beiträge zur elektrophysiologischen Methodik II. Ein vereinfachtes Reizgerät für unabhängige Veränderung von Frequenz und Dauer der Impulse. *Helv. Physiol. Acta*, **1950**, *8*: 18-24.

Reference: GANGLOFF, H. and MONNIER, M. The action of anticonvulsant drugs tested by electrical stimulation of the cortex, diencephalon and rhinencephalon in the unanesthetized rabbit. *EEG Clin. Neurophysiol.*, **1957**, *9*: 43-58.

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LES VARIATIONS DE LA PRESSION ARTÉRIELLE PROVOQUÉES PAR LES CRISES D'ÉPILEPSIE

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INTRODUCTION

La conception d'un contrôle du tonus vasomoteur par l'écorce cérébrale est fondée sur différents arguments, dont les plus anciens et les plus souvent invoqués ont été déduits d'expériences de stimulation. François-Franck signale que Vulpian, dès 1875, insistait dans son cours de démonstration sur la constance des réactions circulatoires provoquées par l'électrisation du gyrus sigmoïde, et qu'il donna à Bochefontaine l'idée d'en poursuivre l'étude. En fait, une série de publications ne tardèrent pas à voir le jour, se succédant à cadence rapide jusque vers 1900, émanant de Danilewski (1875), Bochefontaine (1876), Eulenburg et Landois (1876), Ch. Richet (1878), François-Franck (1887), etc....; tous ces mémoires s'accordent pour conclure que la faradisation de l'écorce motrice détermine, par vaso-constriction, une hausse de la pression artérielle. Puis, après une période d'expérimentation ralentie, la question retrouve l'actualité en 1927 avec la publication de Dusser de Barenne et Kleinknecht qui, relatant des résultats inverses, inaugure une période non encore terminée d'opinions discordantes: les uns, à la suite de ces auteurs, inclinent à considérer l'aire motrice comme "dépressive", voyant la tension baisser sous l'effet de sa stimulation (Hsu, Hwang et Chu 1942; Morin et coll. 1948; Kremer 1948), alors que beaucoup d'autres, plus nombreux, obtiennent de l'hypertension et la décrivent comme "pressive" (Spiegel et Hunsicker 1936; Crough et Thompson 1936; Hoff et coll. depuis 1936, etc....), sans parler des opinions intermédiaires.

Cependant tous ces travaux ont été effectués dans des conditions expérimentales bien particulières: jusqu'en 1900, la curarisation de l'animal et l'absence d'anesthésie étaient la règle. Les conséquences épileptogènes de la faradisation corticale ne pouvaient être mises en évidence que par l'observation de composantes végétatives non abolies par le poison, ou par des procédés spéciaux, tel que la perfusion d'une patte postérieure de l'animal avec du sang défibriné de façon telle qu'elle ne subisse pas la curarisation et signale l'invasion épileptique par des contractions (François-Franck 1887).

Les travaux plus récents au contraire ont été effectués avec des animaux anesthésiés, en général profondément, et chez lesquels, par conséquent, le seuil épileptique est considérablement augmenté. Mais aucun des chercheurs ne s'est inquiété des crises éventuellement provoquées par les stimulations, crises inapparentes à cause de la curarisation employée conjointement à l'anesthésie. Nos recherches portaient initialement sur les centres vasomoteurs corticaux, et n'étaient pas orientés au départ vers l'épilepsie; mais ayant rencontré l'hypertension liée aux épilepsies corticales, nous avons essayé (avec des moyens améliorés) de déterminer ses caractéristiques, ses conditions, et, si possible, sa signification, estimant qu'il était logique d'utiliser le type particulier d'activation que constitue l'épilepsie pour faciliter une première "approche" du problème des centres vasomoteurs corticaux.

TECHNIQUE GÉNÉRALE ET MÉTHODE DE TRAVAIL

Nos expériences, toutes "aiguës", ont été effectuées sur 125 chiens, mâles ou femelles, adultes, d'un poids variant de 8 à 20 kilos.

1° *Préparation de l'animal.*

L'animal est tout d'abord endormi à l'éther (le plus souvent à l'aide d'un appareil à circuit fermé Heidbrink) et demeure anesthésié pendant tout le temps opératoire. Puis il est placé dans un appareil du type Horsley-

Clarke (modifié par Paul Dell) qui sert à la contention de la tête. Le temps opératoire comporte:

la mise en place d'une canule trachéale,

la dénudation d'une grosse artère (fémorale de préférence ou carotide) dans laquelle est placée une canule de François-Frank,

une crâniectomie uni ou bilatérale, exposant largement la convexité et s'approchant le plus possible de la ligne médiane. Si nécessaire, un rein est placé dans un oncographe. L'anesthésie n'est, en général, pas poursuivie au-delà de 45 min.; puis l'animal est curarisé à dose paralysante dès les premiers signes de réveil (Flaxédil [1]); il est alors placé sous respiration artificielle jusqu'à la fin de l'expérience.

Quelques animaux ont été opérés sous anesthésie locale plan par plan à la Xylocaïne; les résultats obtenus dans ce cas ont été analogués à ceux fournis par la technique habituelle.

Enfin, nous avons vérifié sur un petit nombre d'animaux que les résultats ci-dessous décrits peuvent être obtenus sans curarisation. Celle-ci n'est utilisée que comme un moyen d'obtenir les différents enregistrements dans d'excellentes conditions techniques.

2° *Deux types d'enregistrements* sont toujours effectués simultanément:

a) Sur papier enfumé sont inscrits:

la pression artérielle au moyen du kymographe de Ludwig,

l'électrocorticogramme, au moyen d'une à six dérivations d'un appareil EEG Alvar,

parfois le volume d'un rein à innervation intacte et d'un rein énervé,

le temps, sous forme d'un signal chaque 15 sec.,

les stimulations.

Le cylindre enregistreur tourne à la vitesse de 17,5 mm par minute.

b) Simultanément on enregistre, au moyen de la machine EEG à la vitesse normale de 15 mm/sec., les mêmes dérivations électrocorticographiques que sur le papier enfumé. Les potentiels corticaux sont recueillis au moyen d'un "peigne" comportant des électrodes souples en fil d'argent de 6/10 mm, terminées par une petite boucle d'argent chloruré afin de ne pas blesser le cortex.

Enfin, une des dérivations de cet appareil EEG enregistre l'électrocardiogramme (en D II) permettant ainsi de vérifier la fréquence cardiaque.

3° *Les stimuli épileptogènes* utilisés ont été nombreux et variés:

Les stimuli électriques ont consisté:

en courant faradique fourni par un charriot de Dubois-Reymond (Harvard-inductor);

en courant sinusoïdal à 50 c/sec. amené à la valeur convenable au moyen d'un potentiomètre de faible résistance;

en courants carrés, réglables en fréquences, durée et amplitude, fournis par des stimulateurs électroniques (stimulateur Vigne-Corriol, stimulateurs Grass, stimulateur Racia). La stimulation est effectuée dans la plupart des cas à tension constante, au moyen de deux électrodes d'argent chloruré séparées de quelques millimètres et appliquées sur le cortex.

Il a été fait appel à la strychnisation locale du cortex, combinée avec la stimulation sensorielle ou avec la faradisation corticale pour déclencher des crises à généralisation progressive et orientée.

La strychnisation a été effectuée dans tous les cas au moyen d'un confetti de papier filtre imbibé de soluté de strychnine à 1 pour cent dans du sérum physiologique, et déposé sur le cortex à l'endroit convenable. Lorsqu'il était nécessaire de strychniser une zone étendue, le cortex d'abord séché au papier filtre était ensuite badigeonné au moyen d'un pinceau souple avec le soluté de strychnine.

Le déclenchement d'une post-décharge extensive sur le cortex ainsi préparé a été réalisé soit par stimulation électrique ménagée (par l'un des procédés décrits plus haut), soit en réalisant une "épilepsie de Clémenti". Pour ce faire, la strychnisation a porté sur l'aire réceptrice visuelle primaire d'un des hémisphères; les yeux de l'animal ont ensuite été soumis aux éclairs lumineux, répétés 15 fois par seconde, d'un stroboscope électronique de haute puissance (Varéclat Alvar).

[1] Curarisant de synthèse = triiodoéthylate de tri (β-diéthylaminoéthoxy) 1-2-3 benzène.

L'épilepsie d'Amantea n'a pu être employée car les stimuli sensitifs forts chez l'animal curarisé non endormi sont dolorigènes, et modifient le tonus vaso-moteur par voie réflexe.

Enfin, nous avons également fait appel au Pentétrazol [1] injecté soit rapidement dans les veines à dose forte et à des concentrations élevées de 5 à 10 pour cent pour provoquer des crises généralisées d'emblée et durables, soit en injection lente pour susciter ensuite des crises photo-cardiazoliques par stimulation stroboscopique des yeux.

ÉTUDE DES CORRÉLATIONS ÉLECTRO-KYMOGRAPHIQUES

Les animaux ainsi préparés montrent des tracés électroencéphalographiques d'éveil; lorsqu'ils ont subi plusieurs crises épileptiques généralisées, les tracés inter-critiques s'altèrent et montrent des ondes lentes et irrégulières, d'assez forte amplitude, entrecoupées de ''bursts'' rapides à 15 c/sec., de brève durée. Ces anomalies post-critiques sont d'autant plus importantes que les crises sont plus longues et plus rapprochées: elles semblent peu réversibles, lorsqu'un certain état a été atteint.

La pression sanguine de ces animaux est en général élevée (16 à 18 cm de mercure), et leur fréquence cardiaque rapide (150 à 230 battements par minute) par l'action vagolytique du Flaxédil aux doses employées. Il arrive parfois qu'en début d'expérience la tension artérielle soit instable et présente des oscillations lentes, irrégulières et en tout cas sans périodicité, pouvant atteindre 5 ou 6 cm de mercure; ces oscillations spontanées, augmentées par les bruits et les variations de lumière en particulier, semblent en rapport avec le ''stress'' que subit un animal éveillé et curarisé; elles s'atténuent en général après une ou deux crises généralisées; dans quelques cas, elles compromettent l'expérience.

Signalons enfin que nous n'avons pu établir de corrélations valables et constantes entre le niveau de la pression artérielle intercritique et les caractères des électrocorticogrammes.

[1] Pentaméthylène-tétrazol, ou Cardiazol, ou Métrazol.

1° *Caractères généraux des réponses pressives au cours des crises généralisées.*

Chez les animaux préparés soit sous anesthésie locale, soit sous éthérisation de courte durée, les corrélations entre la pression artérielle et les décharges épileptiques sont évidentes, constantes et étroites, qu'il s'agisse de crises faradiques ou de paroxysmes provoqués par d'autres moyens. L'embrasement cortical va de pair avec une hypertension artérielle transitoire, contemporaine de la décharge généralisée, et cessant avec elle. Cette hypertension critique peut atteindre une vingtaine de centimètres de mercure, et il n'est pas rare d'enregistrer des pressions atteignant 30 à 35 cm de mercure.

La latence de l'hypertension et sa pente d'établissement varient avec la vitesse d'invasion des décharges électrocorticographiques.

Au cours de l'épilepsie cardiazolique ou photocardiazolique, qui enflamme à peu près simultanément toute l'écorce, la pression fémorale monte quelques secondes seulement après cet embrasement, presque verticalement, et atteint son maximum en quelques systoles (fig. 1). Il en va encore de même des stimulations électriques suffisamment intenses principalement lorsqu'elles affectent la région sigmoïdienne dans laquelle la post-décharge est très rapidement généralisée.

Par contre, lorsqu'on porte à la surface d'un hémisphère une stimulation électrique ménagée, faiblement supraliminaire par rapport au seuil épileptogène, les post-décharges demeurent un temps focales et relativement peu fréquentes; elles n'atteignent la fréquence critique que secondairement. Dans ce cas, si la stimulation concerne l'aire péricruciale, il est possible d'obtenir deux réponses pressives, comme dans la figure 2 où la branche postérieure du gyrus sigmoïde a été stimulée à 18 h. 18 pendant 12 sec. par des ondes carrées (50 c/sec. - 2 msec.) La première réponse, précoce, brève, peu ample est une réponse locale propre à la stimulation. La seconde, comparable à celle qu'a déterminé une stimulation non épileptogène du gyrus sigmoïde, antérieur à 18 h. 15, tardive, ample et persistante, est seule ''épileptique'' et coïncide avec la généralisation de la crise.

On conçoit que si l'intensité du stimulus déclenchant est augmentée, ces deux réponses se confondent. On peut passer de l'un à l'autre type en modifiant les paramètres de stimulation électrique, ou en adjoignant des injections intraveineuses de Pentétrazol à celle-ci.

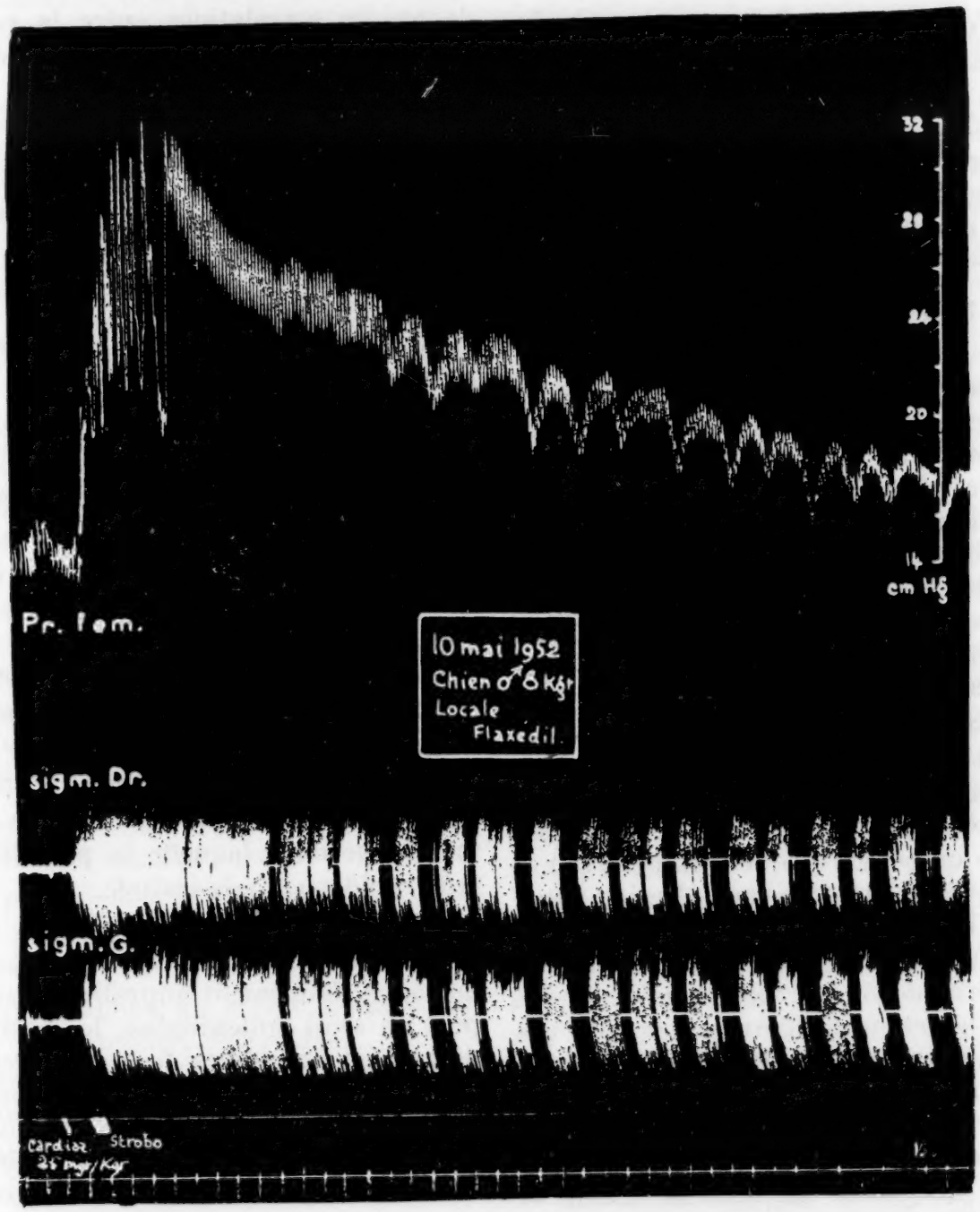

Fig. 1

Crise généralisée déclenchée par éclairement stroboscopique des yeux après injection intraveineuse de 25 mg/kg de Pentétrazol. Noter l'ascension rapide de la pression artérielle dès le début de la crise électrique, simultanée sur les deux hémisphères; les interruptions de la crise se marquent par des chutes et les reprises par des ressauts de la pression.

Pendant toute la durée de la décharge épileptique généralisée, la pression artérielle reste élevée; cependant, si la crise dure plusieurs minutes, il est de règle d'enregistrer un fléchissement lent, continu et progressif de la pression artérielle qui baisse par exemple de 31 cm de mercure au début de la crise généralisée à 21 cm après 6 min de crise (fig. 1).

Il est fréquent, au début des crises brutales et intenses, de constater le phénomène de

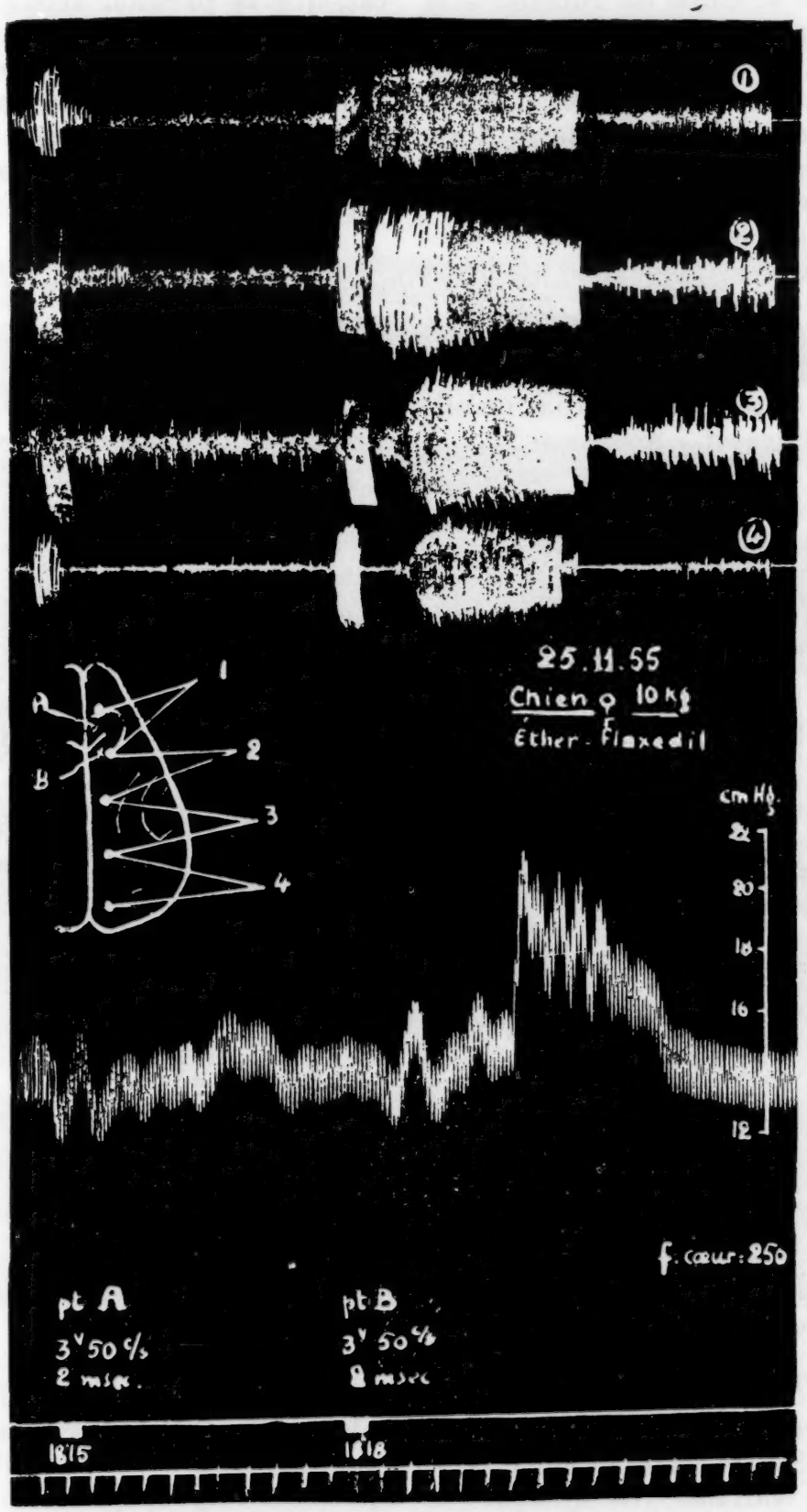

Fig. 2

18 h. 15. Stimulation en A (ondes carrées, 3 V., 50 c/sec., 2 m. pendant 10 sec. Pas de post-décharges. Réponse circulatoire de faible amplitude.

18 h. 18. Stimulation en B (mêmes paramètres). Post-décharges locales et à fréquence basse, puis crise généralisée. Première réponse du type précédent, suivie d'une hypertension plus forte "épileptique".

l'"*action-pulse*" si le chien est curarisé à la tubocurarine. Ce phénomène manque souvent après curarisation au Flaxédil, en raison de son action vagolytique déjà rappelée.

La fin de la crise marque celle de l'hypertension. Lorsqu'elle est soudaine et se manifeste simultanément sur tous les canaux, laissant brusquement place à un silence électrique, comme cela est de règle dans ces types d'épilepsie, la pression artérielle revient à son niveau de départ en moins d'une minute; si l'accès dure plusieurs minutes, elle pourra tomber au-dessous de son niveau initial, qu'elle récupère progressivement.

cas, que la pression artérielle reflète fidèlement l'activité critique du cortex: pendant chaque décharge épileptique la pression artérielle est élevée, mais pendant les silences intercritiques, elle baisse plus ou moins, suivant la durée de l'intercrise, pour remonter dès la reprise des décharges (voir fig. 1).

2° *Effets de l'ordre d'invasion du cortex par la crise épileptique.*

Afin d'évaluer l'importance respective des diverses régions de l'écorce dans l'apparition de l'hypertension épileptique, il convenait de provoquer des crises à extension progressive

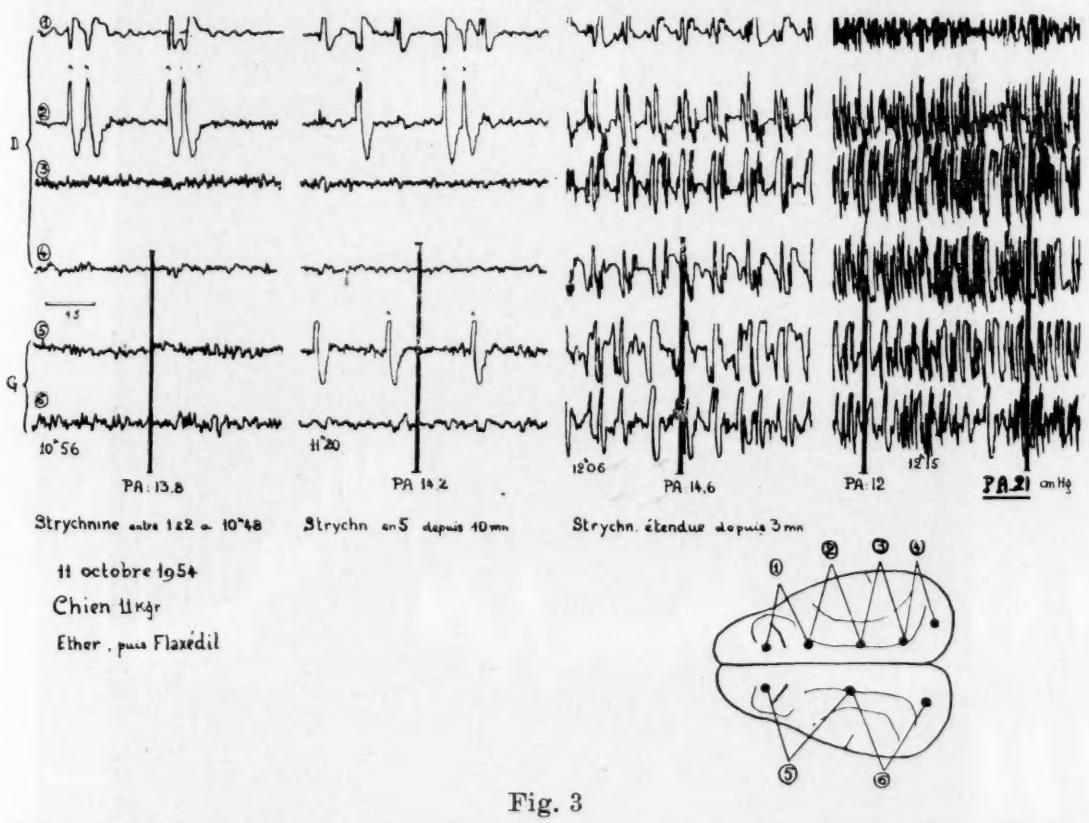

Fig. 3

Strychnisation progressive de l'ensemble de la convexité. Les pointes strychniques non synchronisées sont sans effet sur la pression artérielle; au contraire, à 12 h. 15, la synchronisation se généralise et la pression artérielle passe brutalement de 12 à 21 cm de mercure.

La durée de l'hypertension critique est à peu près égale à celle de la crise épileptique enregistrée par l'électro-corticogramme et, en conséquence, très variable (de quelques secondes à quelques dizaines de minutes).

Les plus longues sont provoquées par l'injection intraveineuse brutale de fortes doses de Pentétrazol susceptibles d'installer une sorte d'état de mal avec des crises généralisées subintrantes, entrecoupées de silences électriques de courte durée. Il se vérifie, dans ces

et dirigée, c'est-à-dire envahissant les hémisphères dans un ordre donné et variable suivant les conditions. Les différents types d'épilepsies strychniques, dont le principe est de créer par badigeonnage local un foyer préférentiel à partir duquel les décharges se généralisent sous l'influence d'un stimulus complémentaire, répond à cet objet.

Aussi, les avons-nous utilisés après avoir étudié les effets propres des pointes strychniques.

a) Effets des pointes strychniques sur la pression artérielle.

Les pointes strychniques localisées sont sans effet sur la pression artérielle, quelle que soit la zone strychnisée. L'étendue de la zone présentant des pointes strychniques asynchrones semble également n'avoir aucun effet

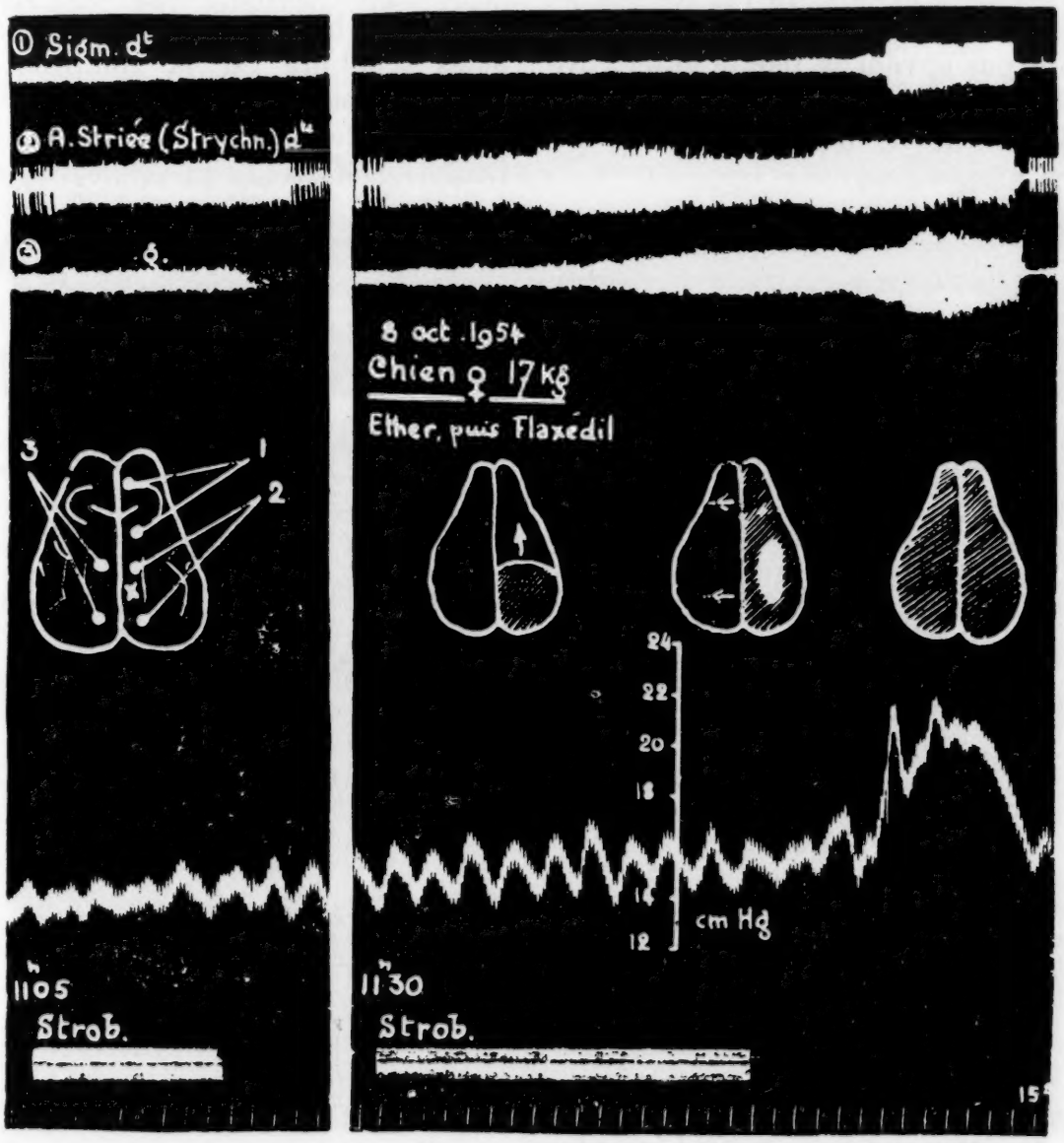

Fig. 4

Epilepsie de Clémenti. A gauche, l'éclairement stroboscopique fait apparaître une crise qui demeure occipitale et sans effet vaso-presseur; à droite, crise focale progressivement généralisée, avec forte hypertension lorsque l'embrasement est total.

presseur. De plus, il a été possible dans certains cas de strychniser l'ensemble de la convexité des deux hémisphères et d'enregistrer les pointes strychniques ainsi provoquées sur tout le cortex exposé, sans pour autant constater des modifications pressives, tant que ces pointes surviennent sporadiquement. Mais il suffit alors d'un stimulus faible pour mettre, pour ainsi dire, "le feu aux poudres"; l'éclairement brutal des yeux, un claquement des mains, une faible stimulation électrique du cortex, suffit à "mettre en phase" les différentes aires corticales. En quelques secondes, les pointes strychniques se synchronisent et font place à une décharge à 16 c/sec. de grande amplitude, généralisée et hypersynchrone. On constate alors, pendant le déroulement de la décharge généralisée, une hypertension en un seul bond, identique à celle déjà décrite. La condition nécessaire à l'occurence de l'hypertension est la synchronisation des décharges,

les pointes asynchrones seules étant sans action sur la pression artérielle (fig. 3).

b) *Effet des crises à point de départ occipital.* (Epilepsie type Clémenti).

L'épilepsie de Clémenti est aisément déclenchée par la stimulation stroboscopique chez un chien dont l'aire striée a été strychnisée. L'expérience prouve que le niveau de pression demeure inchangé, tant que les décharges n'ont pas envahi la partie antérieure des hémisphères.

L'invasion corticale affecte deux modalités:

strychnisé recrute beaucoup plus rapidement dans la région homologue controlatérale et finalement, se généralise brusquement d'arrière en avant sur les deux hémisphères. Dans ce cas, la pression artérielle ne présente qu'un seul bond, de forte amplitude lorsque la quasi totalité du cortex est embrasé (fig. 5).

Ces constatations suggèrent deux interprétations: ou bien l'hypersynchronie critique des pôles frontaux est la condition nécessaire, peut-être même suffisante, pour l'occurence de l'hypertension épileptique; ou bien la participation de toute la corticalité explorée est

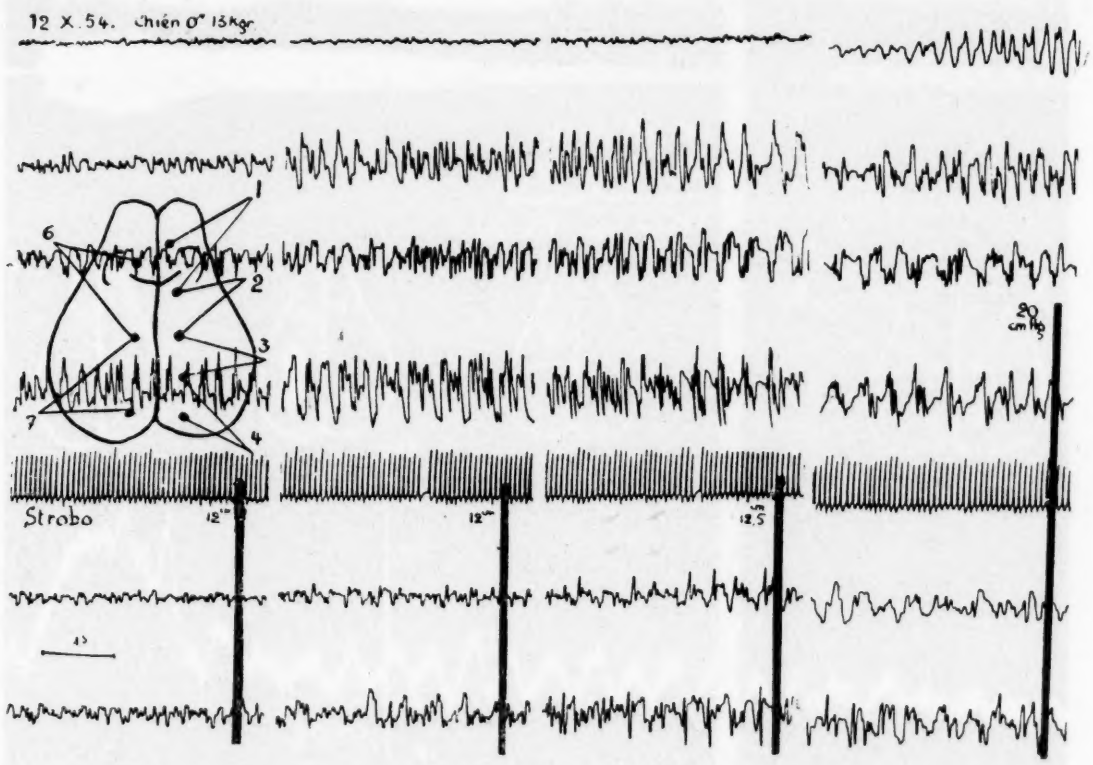

Fig. 5
Epilepsie de Clémenti (strychnisation occipitale droite) à extension progressive à peu près simultanée sur les deux hémisphères. Explication dans le texte.

Dans un premier cas, la crise tend à s'étendre vers le pôle antérieur de l'hémisphère strychnisé; puis, lorsque celui-ci est totalement envahi l'extension se fait très rapidement et transversalement sur la totalité de l'hémisphère opposé. Dans ce cas, la pression artérielle marque une première élévation, en général d'amplitude modérée lorsque la totalité de l'hémisphère strychnisé est embrasé; puis une forte hausse, quelques secondes après l'invasion de l'hémisphère controlatéral (fig. 4);

Dans une deuxième éventualité, la crise qui débute toujours sur le pôle occipital requise, sans qu'aucun territoire cortical joue un rôle prédominant.

c) *Effet des crises à point de départ frontal.*

Pour choisir entre ces deux hypothèses, il a été nécessaire d'effectuer un autre type d'expériences, au cours desquelles l'invasion épileptique chemine en sens inverse, c'est-à-dire du pôle antérieur au pôle postérieur. Nous avons d'abord songé à faire appel à l'épilepsie d'Amantea, que l'on provoque, après strychnisation du cortex sensitivo-moteur, par des stimuli appliqués à la partie du corps correspondante. Mais elle n'est obtenue,

en réalité, que chez des chiens "prédisposés", et cette méthode ne convient pas pour notre expérimentation, car les stimuli sensitifs, chez les animaux curarisés, non anesthésiés, provoquent des variations de tension artérielle en dehors de toute manifestation épileptique. Nous avons donc réalisé *des crises à point de départ antérieur,* par strychnisation (selon la technique habituelle) d'un gyrus sigmoïde; dès l'apparition des pointes strychniques ca-

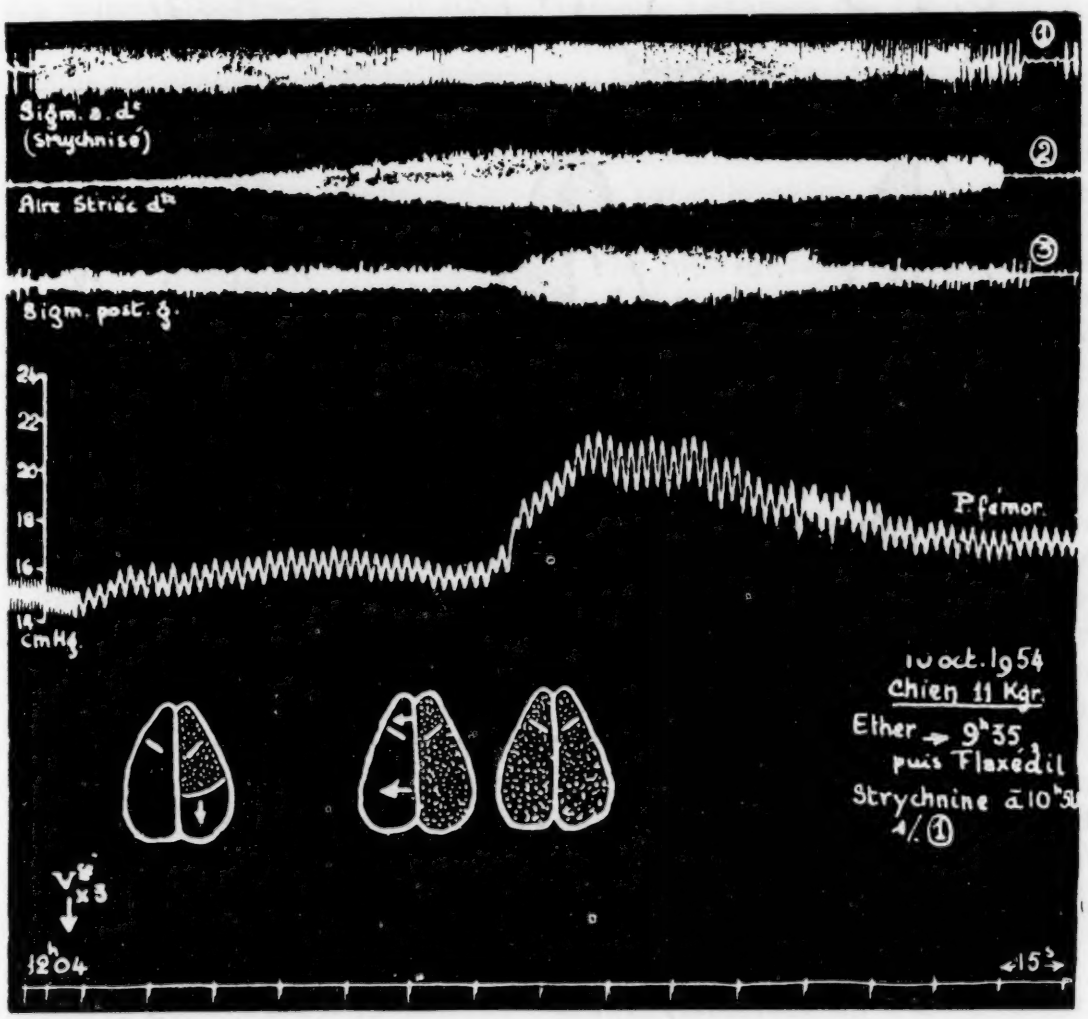

Fig. 6
Crise d'épilepsie consécutive à la strychnisation du pôle frontal droit. Explication dans le texte.

ractéristiques, la crise est déclenchée par une stimulation électrique faible appliquée au gyrus strychnisé. Il en résulte une post-décharge extensive qui évolue selon deux modalités:

Dans un premier cas, l'extension du processus se fait d'avant en arrière sur l'hémisphère stimulé; mais avant l'invasion totale de cet hémisphère, le rôle frontal controlatéral est marquée par un deuxième bond hypertensif, de grande amplitude.

Dans la seconde éventualité, la décharge épileptique envahit d'abord, assez lentement, la totalité de l'hémisphère stimulé; puis, la décharge passe brusquement à l'autre hémisphère qui est envahi dans sa totalité en quelques secondes. Dans ce cas, il n'existe qu'un seul bond d'hypertension qui suit de quelques

secondes l'invasion de l'ensemble du cortex (fig. 6).

A la lumière de ces constatations, il semble donc bien que l'embrasement épileptique des parties postérieures des hémisphères n'est ni suffisant, ni nécessaire, ni cependant indifférent à l'occurence d'une hypertension critique importante. Au contraire, l'embrasement des pôles frontaux joue un rôle plus déterminant que celui du reste du cortex. La parti-

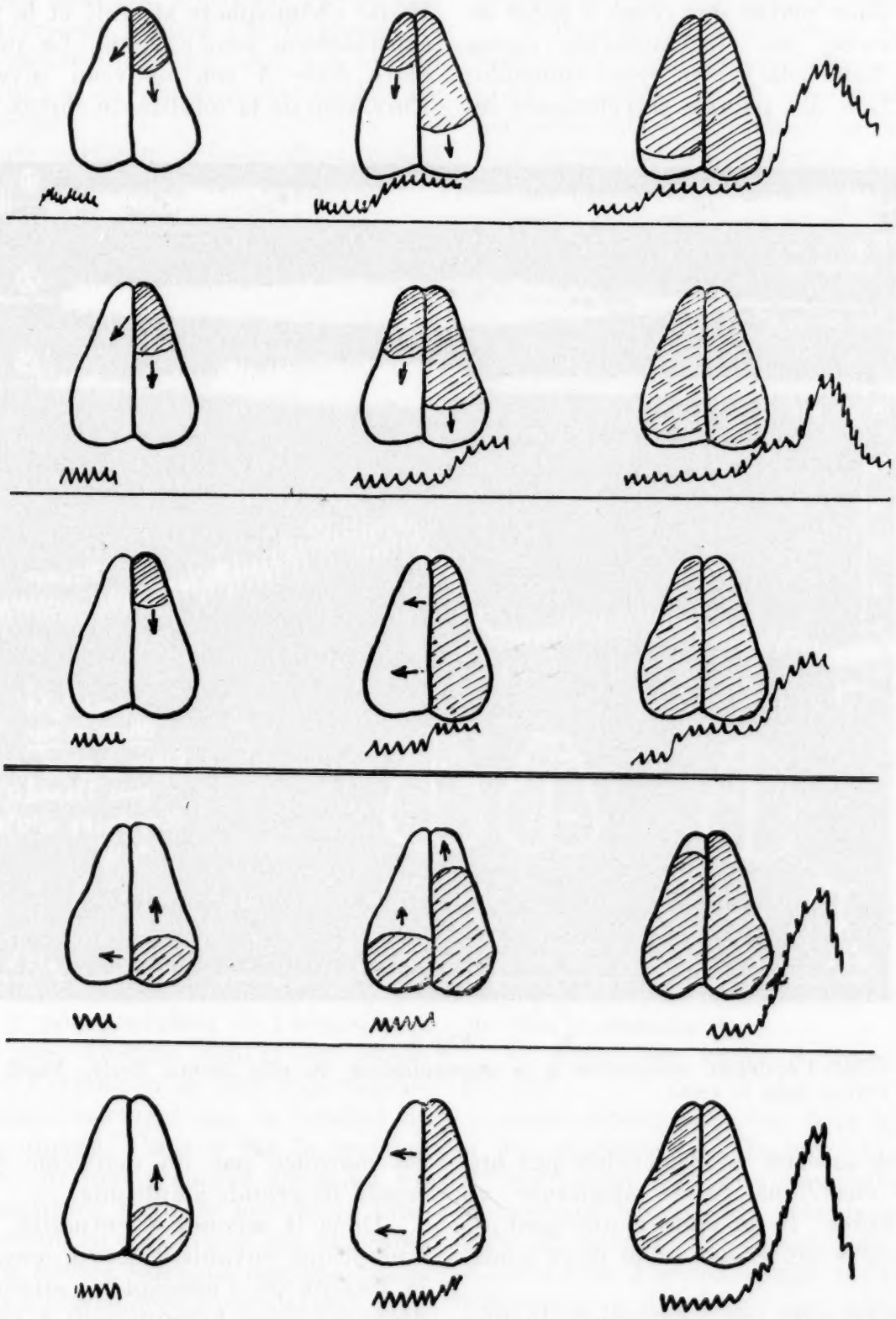

Fig. 7

Schéma résumant les divers modes d'invasion du cortex par des crises d'épilepsie strychnique à point de départ frontal (en haut) et à point de départ occipital (en bas) et leurs incidences tensionnelles.

cipation du cortex frontal des deux hémisphères à l'état épileptique n'est pas toujours une condition suffisante, mais c'est, en tout état de cause, une condition nécessaire au déclenchement d'une hypertension de grande amplitude (fig. 7).

3° *Effet des exclusions corticales.*

La confirmation de ces conclusions a été recherchée dans l'étude des effets qu'exercent diverses exclusions corticales partielles sur l'évolution des crises à propagation progressive et sur leurs incidences tensionnelles; trois types d'exclusions corticales ont été utilisées:

des sections longitudinales portant sur le corps calleux;

des sections corticales transversales rétro-sigmoïdiennes;

des résections du cortex frontal et péri-sigmoïdien.

Ces lésions, et en particulier les ablations corticales, provoquent souvent des perturbations de la pression artérielle de repos; parfois la pression artérielle s'élève notablement (au-dessus de 18 cm de mercure) même en l'absence de crise, devient instable, et des crises spontanées peuvent apparaître de manière désordonnée; dans ce cas, ou bien la pression devient totalement indépendante des corticogrammes, ou bien les ascensions de la pression coïncident avec l'apparition des décharges sur la partie antérieure des hémisphères. Parfois, la pression artérielle tombe (au-dessous de 8 cm de mercure); le seuil épileptique est alors considérablement augmenté, et il devient souvent impossible de provoquer des décharges généralisées; l'injection de sérum physiologique, pour tenter de relever la pression artérielle, provoque parfois l'apparition de crises spontanées, qui disparaissent lorsque la pression diminue de nouveau.

Les expériences de section du corps calleux ont été pratiquées sous contrôle de la vue, latéralement par rapport à la faux du cerveau, au moyen d'un bistouri-mousse, après coagulation des affluents les plus gênants du sinus longitudinal. L'intervention, bien conduite, ne détermine pas d'hypotension artérielle, mais provoque souvent une dépression temporaire de l'activité électrique corticale du côté où les vaisseaux ont été coagulés. L'expérience n'est poursuivie qu'après reprise d'une électrogénèse normale. En fin d'expérience, l'efficacité anatomique des sections a été vérifiée sur pièces et sur coupes.

Avant la section calleuse, l'évolution des crises (provoquées par strychnisation occipitale, combinée soit à des stimulations électriques du cortex occipital, soit à la stimulation lumineuse intermittente des yeux) est celle décrite plus haut à propos de l'épilepsie photique de Clémenti. Après section du corps calleux, l'examen des tracés conduit aux conclusions suivantes:

Dans toute la série d'expériences, le passage de la crise d'un hémisphère à l'autre est encore obtenu. Mais l'évolution des crises est très variable entre animaux, ou même d'un essai à l'autre chez le même animal.

Le plus souvent, la crise se manifeste d'abord seulement sur l'hémisphère strychnisé; puis, progressivement, les électrocorticogrammes controlatéraux montrent un début de recrutement, qui peut soit avorter sans atteindre le niveau critique, soit se poursuivre et aboutir à l'embrasement de l'hémisphère controlatéral. Quelquefois les crises alternent d'un hémisphère à l'autre, et l'embrasement simultané des deux hémisphères semble être fortuit. Mais des décharges généralisées sur les deux hémisphères ont cependant été enregistrées dans des conditions particulières, lorsqu'une stimulation électrique est portée par exemple sur le pôle occipital de l'hémisphère non strychnisé, alors que l'hémisphère strychnisé était déjà dans un état pré-critique.

Dans tous les cas, les crises électriques évoluent indépendamment sur l'un et l'autre hémisphère; même lorsque survient un embrasement simultané de tout le cortex, en aucun cas, nous n'avons constaté une extinction simultanée de l'activité critique des deux côtés à la fois.

Les corrélations entre le kymogramme artériel et les électrocorticogrammes ne sont pas affectées par la section du corps calleux; les ascensions de la pression artérielle sont liées à l'extension des décharges. Les crises monohémisphériques ne s'accompagnent que d'une hypertension modérée et celle-ci débute seulement quand la partie antérieure de l'hémisphère participe aux décharges, alors que déjà les premiers signes de recrutement survien-

nent sur l'hémisphère controlatéral ; l'hypertension s'accentue et atteint son maximum lorsque survient la généralisation de la crise, ou peu avant. La section du corps calleux, en soi, n'exerce donc pas d'influence sur les incidences tensionnelles des crises d'épilepsie (fig. 8).

Les expériences de section corticale ont consisté à isoler l'un ou les deux pôles frontaux par une section transversale du cortex, section pratiquée en arrière du gyrus sigmoïde, de la ligne médiane au sillon ectosylvien, dans un plan frontal ; la section, effectuée par aspiration sous-piale du cortex, après coagulation des vaisseaux les plus gênants, intéresse le cortex et la substance blanche sous-jacente, mais respecte toujours les formations diencéphaliques. Les aires corticales ainsi ''isolées'' ne sont donc plus réunies au cortex postérieur des hémisphères par les connexions courtes cortico-corticales, mais les connexions longues cortico-diencéphalo-corticales sont respectées.

Lorsque la pression artérielle de repos est à un niveau voisin de la normale après la mutilation, les décharges épileptiques à point de départ postérieur sont faciles à obtenir par l'un des procédés déjà décrits.

Une trans-section unilatérale n'empêche pas l'extension des crises au pôle frontal isolé, mais cette extension est toujours retardée. Lorsqu'elle se produit, l'invasion du cortex situé en avant de la lésion est brutale ; elle détermine l'apparition de l'hypertension artérielle.

Les résultats fournis par les trans-sections corticales portant à la fois sur les deux hémisphères sont plus difficiles à interpréter, car elles ont toutes été combinées à des sections calleuses ; cependant, il semble que l'hypertension critique apparaît seulement après l'invasion de l'un et de l'autre pôle frontal, en avant des sections transversales (fig. 9).

Les expériences de résection corticale ont été pratiquées par aspiration sous-piale du cortex sigmoïdien et périsigmoïdien, après coagulation au bistouri électrique ; la lésion a été aussi étendue que possible vers la ligne médiane, où l'on est limité par la présence du sinus longitudinal, et vers le bas où elle atteint le sillon ectosylvien. Dans presque tous les cas, la résection corticale, d'abord unilatérale

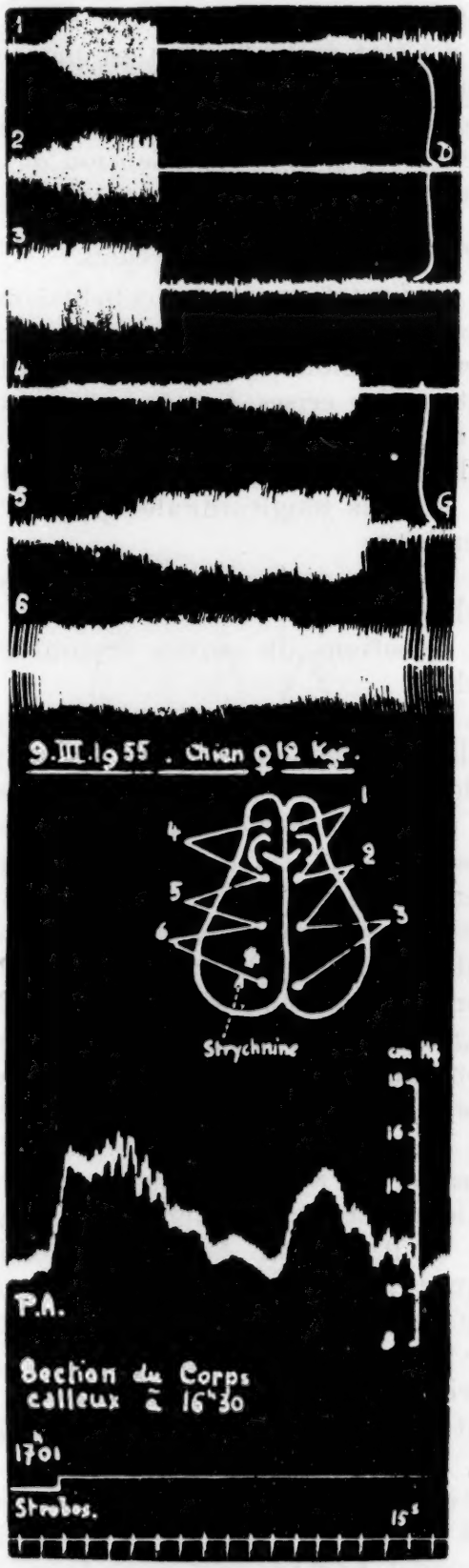

Fig. 8

Crises corticales décalées, à terminaison asymétrique sur les deux hémisphères après section totale du corps calleux. Les deux poussées pressives enregistrées sont contemporaines de l'embrasement de l'un ou de l'autre pôle frontal.

et limitée, a ensuite été agrandie; puis dans un troisième temps, une lésion symétrique a été constituée sur l'hémisphère opposé d'abord respecté.

L'ablation du cortex sigmoïdien sur un seul hémisphère ne fournit pas toujours des résultats univoques; très schématiquement, on peut considérer deux cas en ce qui concerne les crises à point de départ postérieur:

Si la post-décharge se situe sur l'hémisphère qui a subi la mutilation, l'invasion du pôle frontal du côté lésé, en avant de la lésion, ne s'accompagne d'aucune modification significative de la pression artérielle, et celle-ci effectue son ascension seulement lorsque le pôle frontal intact est atteint par l'extension de la crise (fig. 10);

Si, au contraire, la post-décharge initiale prend naissance sur l'hémisphère contro-latéral à la lésion, les corrélations habituelles ne semblent pas modifiées.

Dans ces deux cas, la valeur maxima de l'hypertension critique n'est pas sensiblement affectée par l'ablation corticale.

Lorsque la décortication est bilatérale, au contraire, et à condition qu'elle soit suffisamment étendue, il est possible d'obtenir des crises embrasant l'ensemble de la convexité y compris les deux proréus, sans constater de variation importante de la pression artérielle, qui reste à peu près stable pendant toute la crise généralisée (variations inférieures à 2 cm de mercure) (fig. 11).

4° *Rôle des structures vaso-pressives diencéphaliques.*

Les travaux de Karplus et Kreidl, complétés depuis par de nombreux expérimentateurs, ont montré que la stimulation de très larges zones du diencéphale et du mésencéphale provoque de l'hypertension. La "région vasopressive" diencéphalique comprend toute une série de formations noyées dans la substance réticulaire, ou situées à son voisinage immédiat. C'est pourquoi nous avons été conduits à rechercher à ce niveau le facteur déterminant de l'hypertension épileptique.

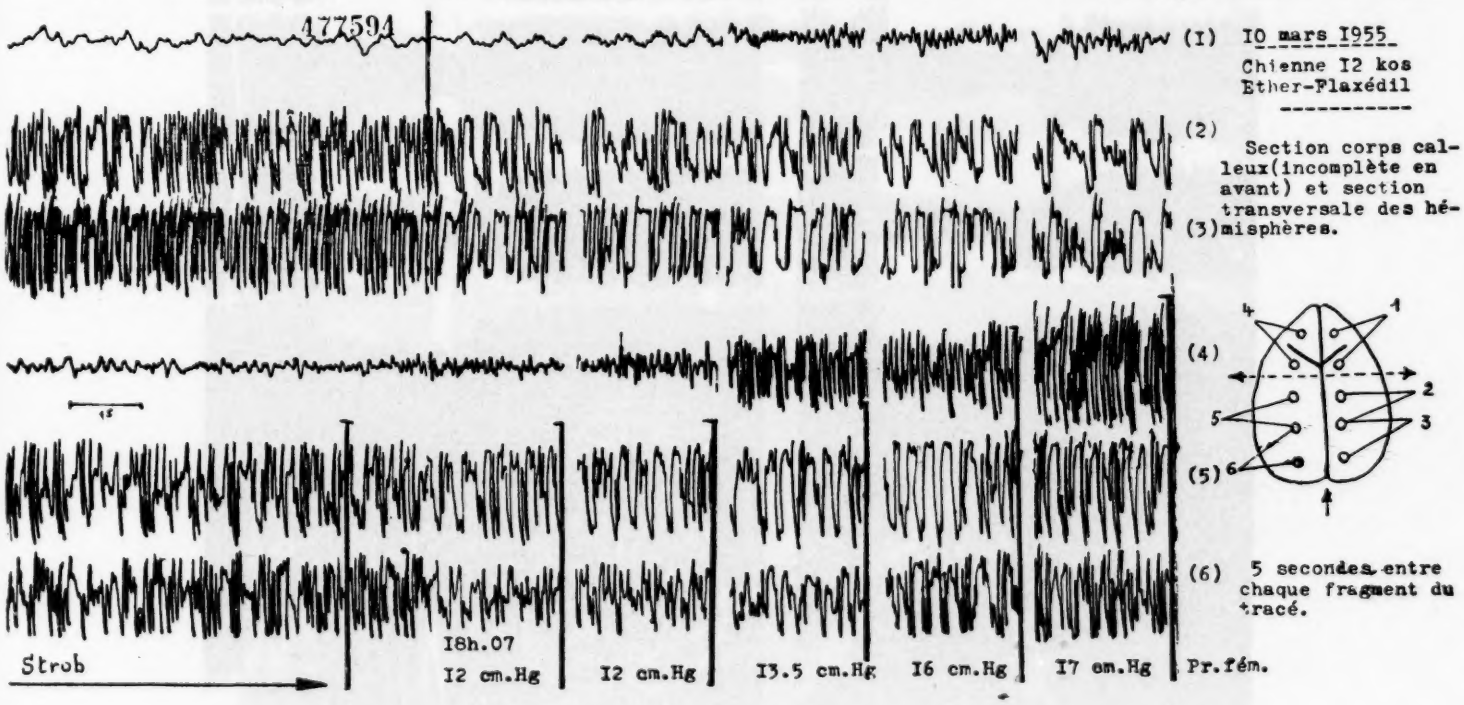

Fig. 9

Propagation d'une crise d'abord occipitale (épilepsie de Clémenti) après section du corps calleux (incomplète en avant) et section transversale rétrosigmoïdienne des deux hémisphères. La pression artérielle amorce son ascension seulement lorsque les deux pôles frontaux (canaux 1 et 4) montrent des signes d'activation.

Cette étude a été effectuée en employant les techniques que nous avons déjà décrites, et en leur adjoignant l'enregistrement des formations diencéphaliques au moyen d'électrodes descendues à ce niveau au moyen d'un appareil stéréotaxique du type modifié par P. Dell. Les coordonnées ont été établies sur le cadavre; les descentes ont été effectuées dans un plan frontal passant à 10 mm en

avant de la ligne unissant les conduits auditifs externes, dans un plan latéral passant 5 mm en dehors de la ligne médiane, jusqu'à 15 mm au-dessus du plan horizontal 0 déterminé par la ligne bi-auriculaire et le bord inférieur des orbites. Avant tout enregistre-

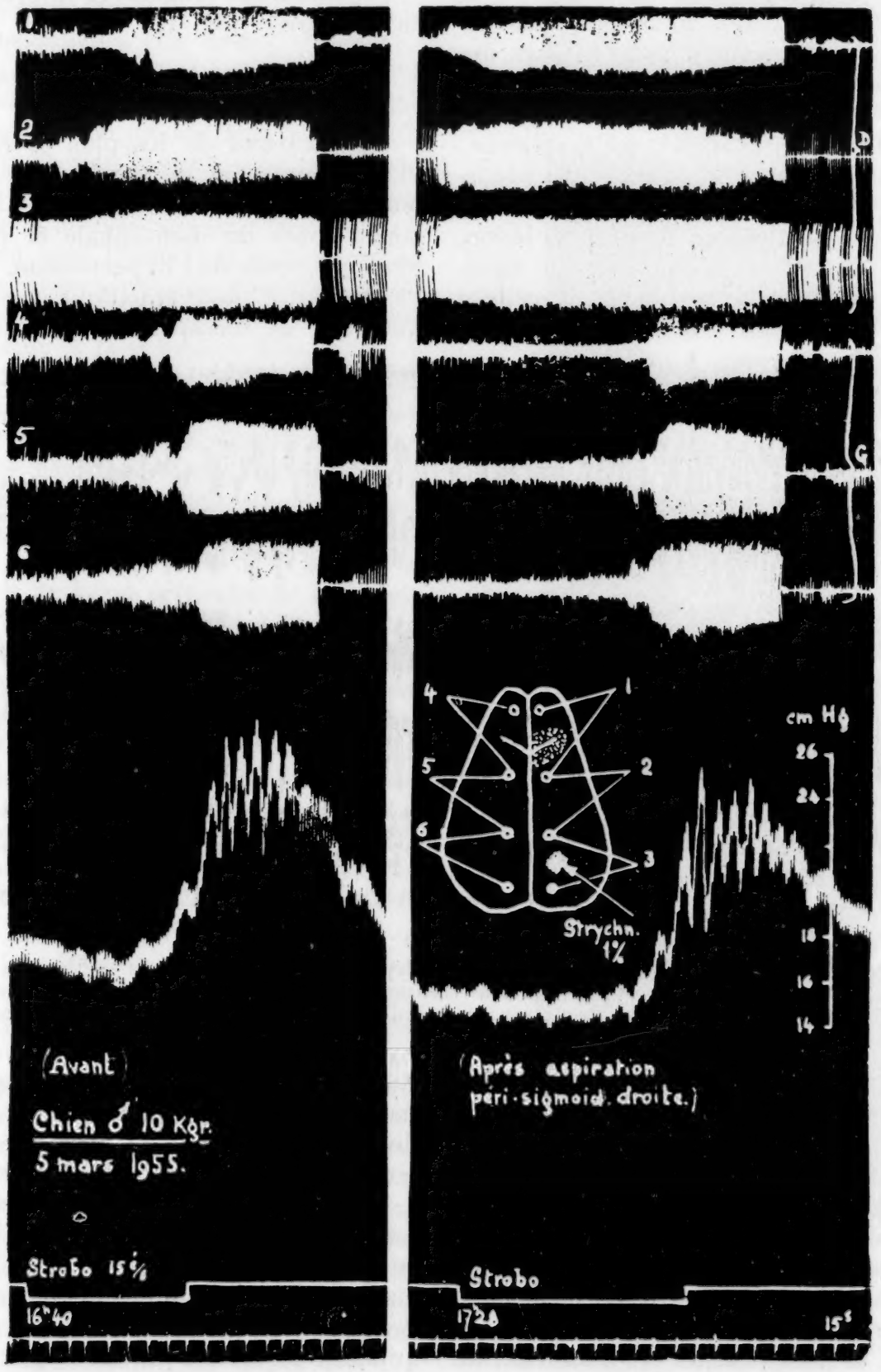

Fig. 10

Effet d'une résection corticale sigmoïdienne unilatérale sur les incidences tensionnelles d'une crise d'épilepsie de Clémenti. Explications dans le texte.

ment et toute stimulation corticale, nous avons chaque fois vérifié la position des électrodes sous-corticales en stimulant le diencéphale à faible voltage, au moyen de ces électrodes. Chez 11 animaux sur les 12 de cette série, la stimulation a toujours provoqué le clocher d'hypertension classique, associé en général à la miction. Les pièces, prélevées en fin d'expérience, ont été incluses à la paraffine et coupées en série; l'examen des coupes a montré que les dérivations diencéphaliques portaient sur la région limitée en avant par le plan frontal passant par les corps mamillaires, dorsalement par le thalamus, en arrière par le plan du noyau rouge, et s'étendant jusqu'au locus niger. Les points les plus souvent atteints se plaçaient dans le sous-thalamus, mais les résultats tensionnels ont été les mêmes pour tous les points.

Au cours des 11 expériences retenues comme valables, les crises ont été provoquées tantôt par stimulation d'un pôle occipital, tantôt par stimulation d'un pôle frontal. Ainsi que le montre la figure 12, dans le premier cas (à gauche) la pression fémorale demeure étale pendant une trentaine de secondes après la stimulation, cependant que la crise ainsi déclenchée affecte seulement la partie postérieure de l'hémisphère ipsi latéral (canal 2), puis controlatéral (canal 5); elle s'élève ensuite progressivement lorsque les décharges se sont déclarées et affirmées dans le

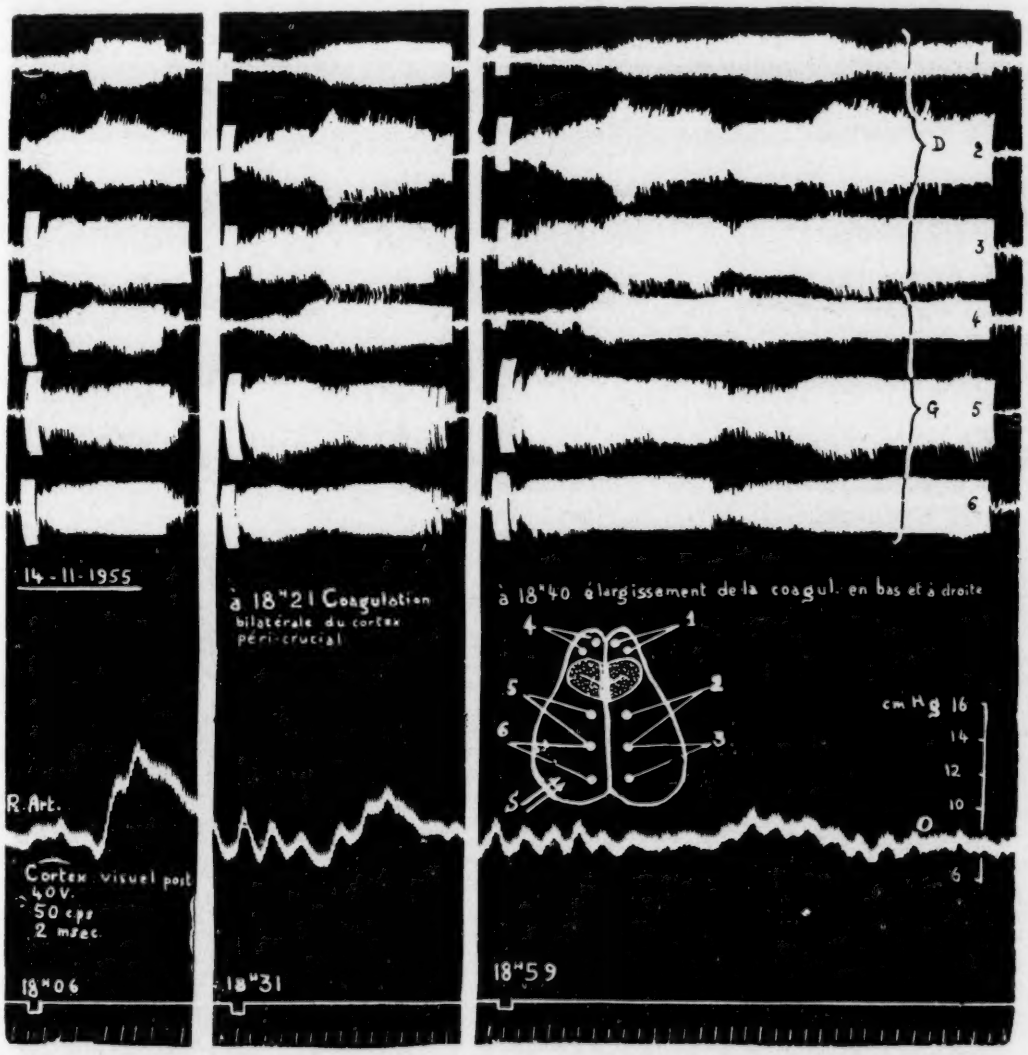

Fig. 11

Crise d'épilepsie par faradisation occipitale. Effets d'une décortication sigmoïdienne bilatérale:

à gauche, avant l'intervention;
au centre, le cortex a seulement été "coagulé" au bistouri électrique;
à droite, il a été procédé à une aspiration sous-piale large des aires sigmoïdiennes.

diencéphale du côté stimulé (canal 3) puis de l'autre côté (canal 6).

Dans les crises à point de départ frontal (à droite de la figure 12), l'hypertension s'établit très rapidement, et très brusquement, marquant l'apparition très rapide des décharges dans le diencéphale ipsi-latéral à la stimulation (canal 6), avec un rebondissement tensionnel au moment de l'invasion du diencéphale controlatéral (canal 3). Ces corrélations sont encore plus apparentes sur le papier de la machine EEG à une vitesse de déroulement 17 fois plus grande.

Il est ainsi confirmé que l'hypertension est liée à l'activation de la région pressive du diencéphale basal et à sa participation à l'hypersynchronie. Mais il est impossible actuellement de faire la part qu'il convient d'attribuer à la substance réticulaire et aux structures qu'elle entoure ou qu'elle avoisine.

5° *Influence des anesthésiques et de la chlorpromazine.*

L'éther, le chloralose, les barbituriques, l'uréthane, à doses anesthésiques, déprime fortement les aptitudes épileptogènes de l'écorce; c'est pourquoi la stimulation électrique sigmoïdienne, répétée à la même intensité, n'exerce plus les effets presseurs constatés avant leur administration, car il est alors impossible d'obtenir des post-décharges extensives et soutenues.

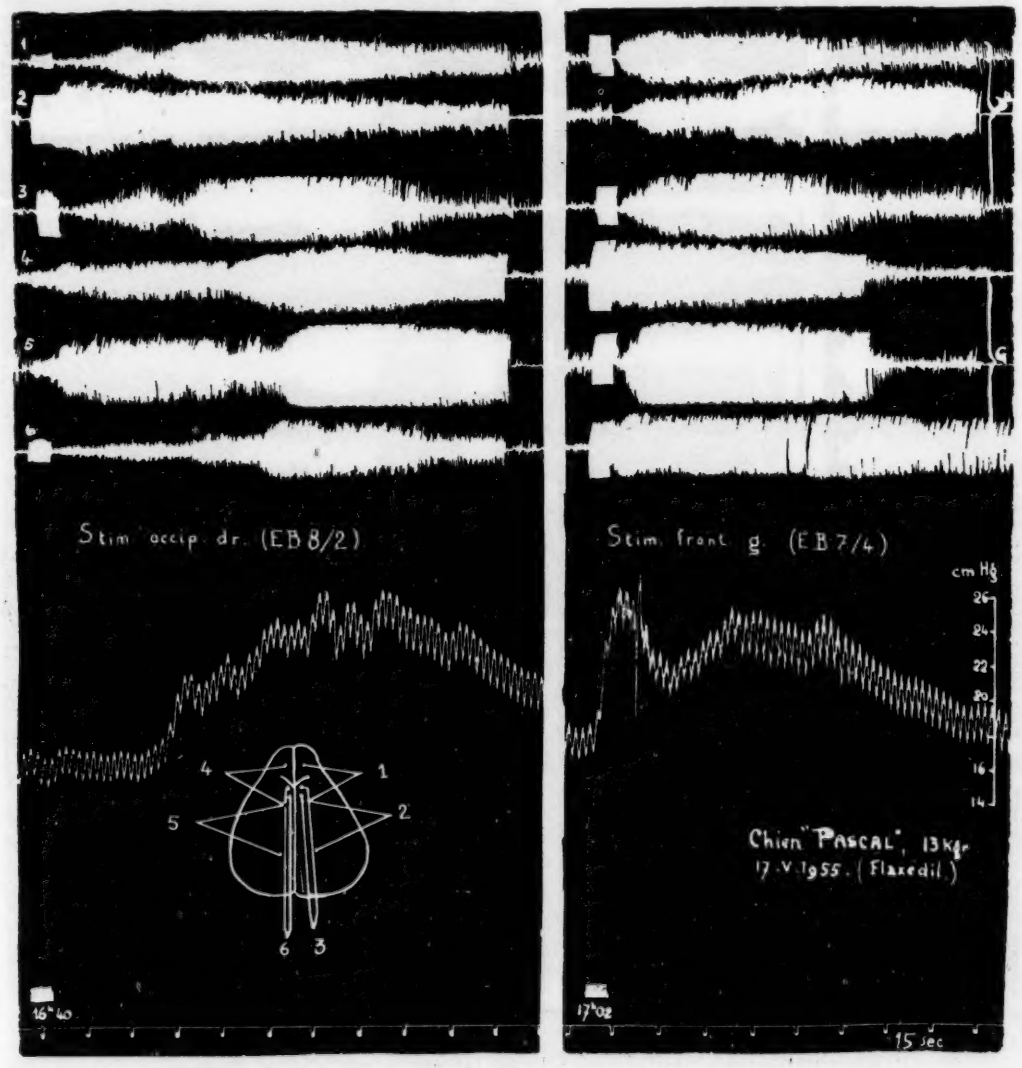

Fig. 12
Crise d'épilepsie par faradisation occipitale droite (tracé de gauche) et frontale gauche (tracé de droite). Explication dans le texte.

En outre, lorsque ces produits sont injectés à doses fortes et sans précautions à un animal déjà curarisé, ils provoquent une chute importante de la pression artérielle intercriti-

que. Mais, à concentration faible, ces divers agents n'empêchent pas la production de crises généralisées prolongées, au cours desquelles on ne constate plus d'effet presseur important; plusieurs heures après l'injection d'une dose anesthésique de chloralose, alors que cet anesthésique a été en grande partie éliminé, la stimulation électrique du cortex produit une crise d'épilepsie extensive et soutenue, avec une hypertension minime. Même avec des anesthésiques à action plus fugace, tels l'éther, il est nécessaire d'attendre au moins une heure après quelques minutes d'anesthésie, pour que la stimulation recouvre à la fois ses effets épileptogènes et presseurs.

Avec les barbituriques et principalement avec le penthobarbital (Nesdonal), qui est très maniable en raison de la rapidité de son action et de son élimination relativement rapide, une action quasi élective a été décelée à des doses très inférieures au seuil anesthésique.

A des doses comprises entre 2 et 3 mg/kg de poids, ce barbiturique ne déprime que légèrement l'excitabilité corticale, de telle sorte qu'en augmentant légèrement l'intensité des stimulations, celles-ci sont parfaitement aptes à produire des crises aussi intenses et aussi prolongées qu'auparavant, mais dont l'effet hypertenseur est annulé ou très fortement diminué (fig. 13).

A des doses encore plus faibles, voisines de 1 mg/kg, administrées en plusieurs fois, les effets épileptogènes ne sont pas diminués à intensité égale des stimulations et parfois même sont prolongés, alors que l'hypertension critique est minime, ou même absente, pendant une ou deux heures.

Injectée dans les veines à des doses de l'ordre de 10 mg/kg la chlorpromazine déprime très fortement l'excitabilité corticale; elle est de plus fortement hypotensive par une action vaso-motrice complexe et déprime la réactivité des muscles artériolaires à l'adrénaline et au médiateur sympathique. Mais, après injection, soit dans les veines à raison de 1 à 3 mg/kg par kilo, soit dans les muscles à raison de 5 à 10 mg/kg, il est possible de déclencher des crises corticales intenses, dont l'effet presseur est annulé ou minime et tardif, par une action centroplégique confirmée. C'est ainsi que dans l'expérience du 8 Décembre 1954 cette réduction manifeste ne pouvait être attribuée ni à la diminution de la pression intercritique peu changée, ni

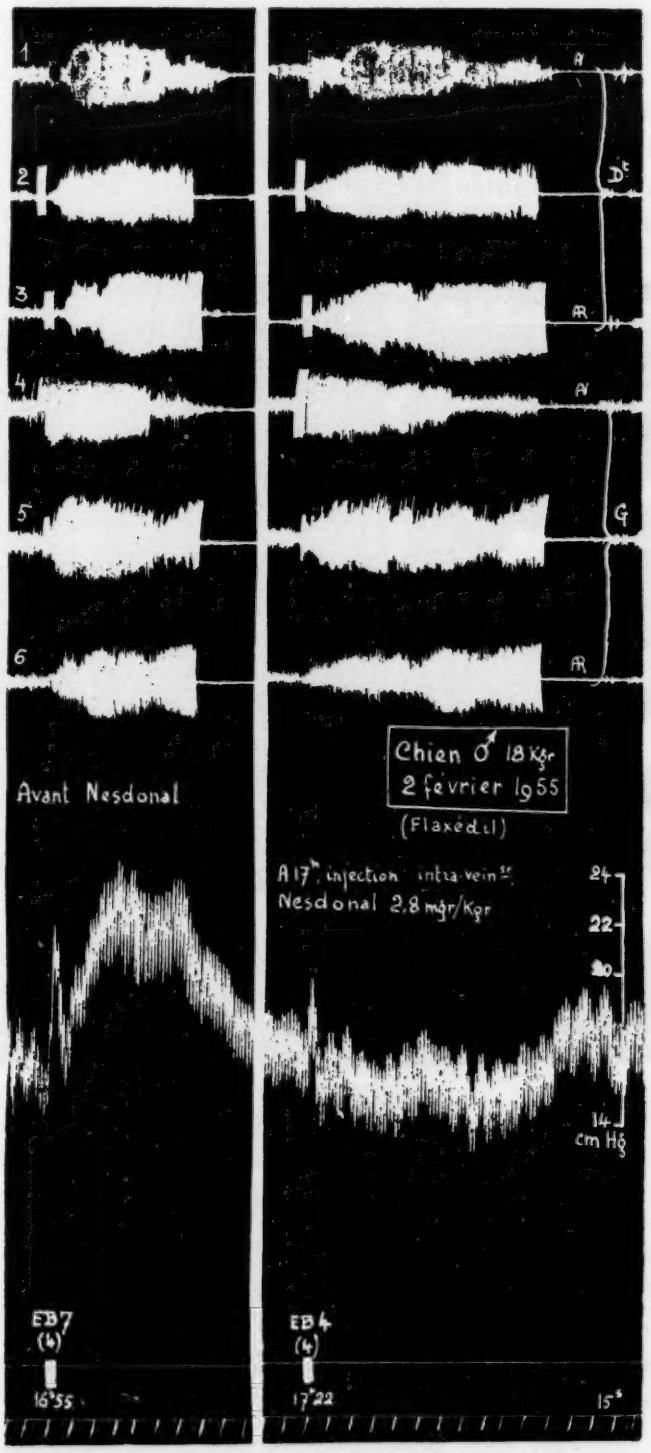

Fig. 13

A gauche, la stimulation électrique du cortex sigmoïdien gauche provoque une crise épileptique, accompagnée d'hypertension artérielle; à droite, après injection de 2,8 mg/kg de penthobarbital (Nesdonal) une stimulation plus forte provoque une crise d'épilepsie prolongée, mais non accompagné d'hypertension.

à celle de la vaso-constriction produite par l'adrénaline ou la nor-adrénaline qui n'étaient pas modifiée. Cette action s'avère lentement et progressivement réversible, en une ou deux heures (fig. 14).

6° *Mécanisme circulatoire de l'hypertension épileptique.*

Deux mécanismes peuvent être responsables de l'hypertension épileptique, si l'on élimine d'emblée les variations de la fréquence cardiaque qui sont faibles ou nulles par suite de l'action vagolytique du Flaxédil. Elle procède essentiellement d'une *vaso-constriction nerveuse généralisée,* puisqu'elle persiste sans modification importante après l'ablation des deux glandes surrénales.

Cette vaso-constriction nerveuse s'accompagne cependant d'une *libération d'adrénaline;* François-Franck (1883) avait déjà observé bien avant la découverte de l'adrénaline, le passage dans la circulation, au cours de "l'épilepsie interne" d'une substance hypertensive. Cette constatation a été ultérieurement confirmée par Molinelli (1926) puis par Tournade et coll. (1939) en utilisant soit la méthode du rein énervé, soit la technique de l'anastomose surrénalo-jugulaire dans des conditions difficiles et sans curarisation; ces auteurs sont d'accord pour conclure que la crise d'épilepsie faradique provoque une augmentation tardive et légère de l'adrénalinosécrétion.

En expérimentant sur l'animal curarisé, et en utilisant l'électrocorticographie pour mettre en évidence les crises d'épilepsie, il est aisé de déterminer avec plus de précision

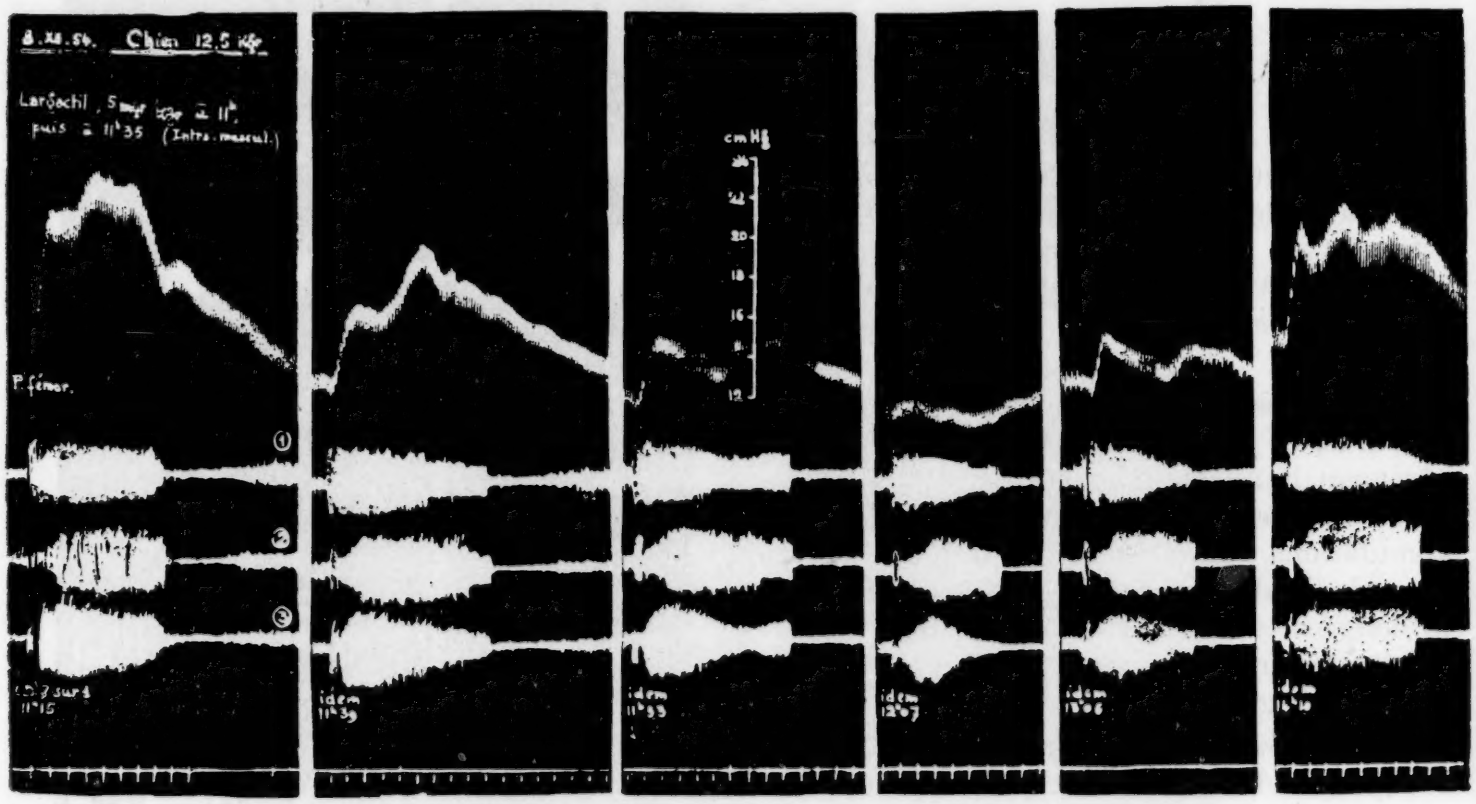

Fig. 14

Injection intramusculaire de chlorpromazine (10 mg/kg au total). Réduction progressive et réversible de l'hypertension contemporaine des crises (faradiques) dont la durée n'est pas diminuée.

les corrélations entre la crise corticale, l'hypertension et la décharge d'adrénaline, en inscrivant le volume d'un rein à innervation intacte et celui du rein énervé, préparés sous anesthésie générale à l'éther, avant de procéder aux stimulations épileptogènes.

Les documents ainsi recueillis montrent une diminution du volume du rein énervé survenant de 20 à 30 sec. après celle du rein intact, attestant de l'accroissement de la sécrétion médullo-surrénalienne au cours des crises corticales intenses, généralisées et prolongées. Par comparaison avec les effets de

doses connues, la quantité d'adrénaline mise en circulation est de l'ordre de 1 à 3 microgrammes par kilogramme de poids (fig. 15). Au cours des crises, même généralisées, mais dont la durée est inférieure à 60 ou 80 sec., l'effet adrénalo-sécréteur est faible, comme d'ailleurs l'hypertension elle-même.

Quant à l'épilepsie tétrazolique, dans les mêmes conditions, et toutes choses étant égales par ailleurs, elle produit une décharge d'adré-

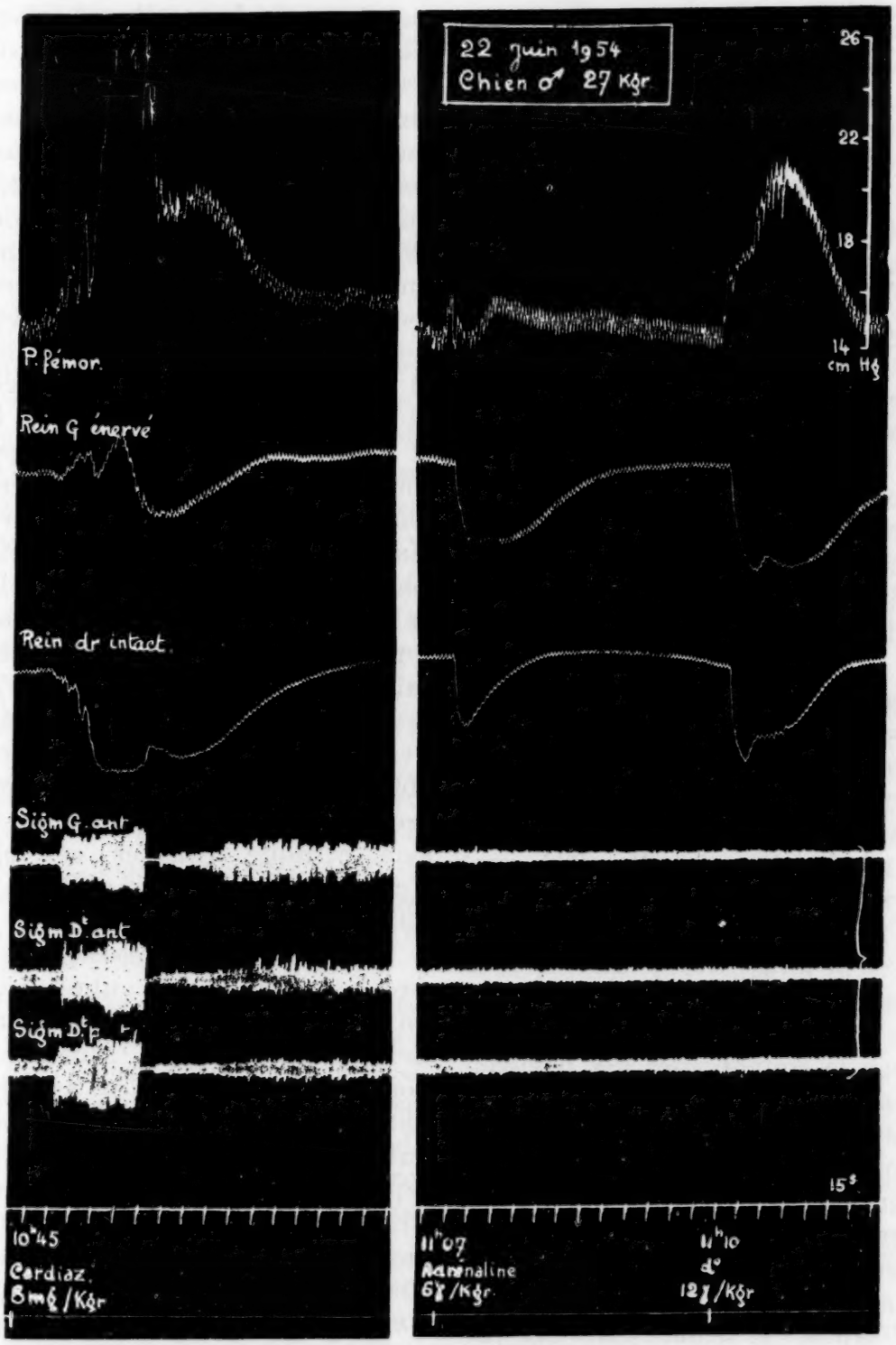

Fig. 15

Mise en évidence de l'adrénalino-sécrétion au cours d'une crise épileptique provoquée par injection intraveineuse rapide de pentétrazol; remarquer la contraction précoce (d'origine nerveuse) du rein droit à innervation intacte et la contraction tardive (d'origine hormonale) du rein gauche énervé. Le tracé de droite permet une approximation de la quantité d'hormone mise en circulation.

naline plus forte que l'épilepsie faradique; à doses non convulsivantes, le pentétrazol intensifie également les effets presseurs et adrénalino-sécréteurs de l'épilepsie, quelle que soit son origine.

DISCUSSION

Les différentes constatations effectuées appellent quelques commentaires et quelques déductions:

Des décharges discontinues lentes, ou arythmiques, telles que celles fournies par la strychnisation superficielle, même étendue, voire généralisée, de la convexité hémisphérique, laissent la pression artérielle étale tant que ne se déclenche pas un paroxysme épileptique généralisé et organisé, c'est-à-dire constitué par des décharges rapides et continues à 15 c/sec. Cette première constatation suggère que l'activation des centres vaso-moteurs s'effectue par l'intermédiaire d'un système doué d'une inertie importante et dont l'activation requiert une sommation temporelle des influx d'origine corticale;

Des décharges répondant aux critères que nous venons d'énoncer, sont sans effet important sur la pression artérielle, si elles demeurent localisées; il est nécessaire, pour obtenir une hypertension critique, que la totalité du cortex exploré soit embrasé par le processus épileptique. Sans doute, l'invasion des deux pôles frontaux et d'une partie notable du reste des hémisphères est-elle déjà susceptible de se marquer par une ascension du kymogramme fémoral; mais l'hypertension s'affirme seulement lorsque toute la convexité participe au paroxysme. Tout se passe comme si l'inertie des centres vaso-presseurs devait être vaincue par la convergence des bombardements provenant d'un système dont les origines corticales sont diffuses;

La condition nécessaire (mais non suffisante) de l'occurence d'une hypertension critique réside dans l'embrasement des aires centrées sur le gyrus sigmoïde; l'hypertension ne se produit pas lorsque ces territoires corticaux ont été détruits. Il semble donc logique d'en déduire que le cortex sigmoïdien joue un rôle prédominant, sans doute parce qu'à son niveau les origines corticales des voies à destination pressive sont plus nombreuses et plus denses.

Cette hypothèse est appuyée par l'étude du retentissement diencéphalique des crises corticales: l'invasion des formations dont la stimulation directe manifeste des effets presseurs s'effectue presque parallèlement à celle du cortex frontal. L'ascension de la pression artérielle au cours des crises progressivement généralisées s'effectue d'autant plus brutalement que ces formations diencéphaliques sont elles-mêmes plus rapidement envahies et participent au processus d'hypersynchronie au moment où l'hypertension se déclare. Ces faits sont à rapprocher de nos connaissances sur les propriétés, la constitution et les connexions de cette région avec l'écorce cérébrale: dès 1935, Kabat, Ranson et Magoun envisageaient que la conduction des effets presseurs s'y effectuait par des chaînes de neurones courts; cette structure, confirmée en ce qui concerne la substance réticulaire, rendrait compte de la nécessité d'une sommation à la fois spatiale et temporelle des décharges pour aboutir à une hausse de la pression artérielle. Par ailleurs, les données établies par les méthodes classiques comme par les méthodes électrophysiologiques et concernant l'origine corticale des projections à destination des noyaux du tronc cérébral et de la substance réticulaire, leur recouvrement dans l'hypothalamus, le diencéphale et le mésencéphale, s'accordent avec ce que nous avons constaté à propos du rôle prédominant de l'embrasement des pôles frontaux dans l'établissement de l'hypertension critique (Jasper et coll. 1951-1952; French et coll. 1955; R. Hernández-Peón 1955).

Ces diverses données sont également à rapprocher de la grande vulnérabilité du système en question à l'égard des substances qui tendent à bloquer les transmissions interneuronales, telles que les anesthésiques et la chlorpromazine; même aux doses faibles, insuffisantes pour diminuer les aptitudes épileptogènes de l'écorce cérébrale, ces produits diminuent fortement ou annulent l'hypertension épileptique, de façon réversible et dans une certaine mesure sélective, bien que les paroxysmes soient aussi intenses et prolongés qu'avant l'administration des drogues.

Au terme de ce travail, nous conviendrons bien volontiers que l'emploi de crises d'épilepsie pour activer les centres vaso-moteurs n'est qu'une caricature grossière de la mise en jeu normale de ces centres. Ce mode d'activation inhabituel, s'il est de quelque intérêt

pour le clinicien, ne saurait être négligé par le physiologiste. Les phénomènes observés doivent correspondre à des processus beaucoup plus nuancés, par là même beaucoup plus difficiles à mettre en évidence et à analyser. C'est pourquoi nous avons cru commode d'utiliser les conséquences vaso-motrices de l'épilepsie comme un premier moyen de débrouiller le problème de l'action des stimulations corticales sur la vaso-motricité, problème que nous aborderons ultérieurement par l'emploi de stimuli non épileptogènes, et dans des conditions aussi voisines que possible des conditions physiologiques.

RÉSUMÉ

Dans le cadre des recherches effectuées sur l'existence d'un contrôle cortical du tonus vasomoteur, nous avons étudié les variations de la pression artérielle au cours des crises corticales généralisées. Chez l'animal curarisé et éveillé:

1° La crise d'épilepsie provoque une hypertension importante, débutant avec la généralisation de la crise et se terminant avec elle; la nature du stimulus épileptogène n'intervient pas dans le déterminisme de cette hypertension.

2° Dans les crises à généralisation progressive, l'invasion des pôles frontaux est la condition nécessaire mais non suffisante de l'hypertension, comme le montrent l'utilisation des crises à points de départ variés et diverses expériences d'exclusion corticale.

3° L'occurrence de l'hypertension artérielle au cours de la crise d'épilepsie est liée à l'activation de la ''région pressive du diencéphale basal'' et à sa participation à la crise.

4° Cette activation est empêchée par de faibles doses d'anesthésiques ou de chlorpromazine, alors que la crise corticale n'est pas modifiée.

5° Le mécanisme périphérique de l'hypertension est constitué par une vaso-constriction nerveuse accessoirement accompagnée de libération d'adrénaline.

6° Ces différents résultats sont discutés et interprétés: une sommation temporelle et spatiale des influx sur la région vaso-pressive du diencéphale basal est indispensable pour obtenir l'hypertension épileptique.

SUMMARY

In the course of research carried out investigating the cortical control of the vasomotor tonus the authors have studied the variations of the arterial pressure during generalized cortical seizures in the curarized and awake animal:

1. The epileptic attack produces a marked hypertension starting with the generalization of the seizure and terminating simultaneously with it. The nature of the epileptogenic stimulus does not influence this hypertension.

2. In attacks with a progressive generalization of the seizure the involvement of the frontal pole seems to be the necessary condition for development of this hypertension, although it is not in itself sufficient to produce it. This is shown in experiments with seizures originating from various locations and also in several experiments with cortical lesions.

3. The occurrence of arterial hypertension during an epileptic seizure is dependent upon the ''pressor area of the basal diencephalon'' which has to participate in the seizure discharge.

4. This diencephalic activation is inhibited by small doses of anaesthetics or chlorpromazine, which do not by themselves modify the cortical seizure.

5. The peripheral mechanism of hypertension is dependent upon neurogenic vaso-constriction, which may be accompanied by liberation of Adrenaline.

6. These results are discussed and interpreted: Temporal and spatial summation of impulses impinging upon the basal diencephalic pressor area is required to produce the epileptogenic hypertension.

BIBLIOGRAPHIE

AJMONE-MARSAN, C. and STOLL, J. J. Subcortical connections of the temporal pole in relation to temporal lobe seizures. *Arch. Neurol. Psychiat.*, Chicago, **1951**, *66*: 669-686.

ALBE-FESSARD, D., BUSER, P. et MINZ, B. Sur une particularité de l'activité électrique chez le lapin thyréoprivé chronique. *C. R. Acad. Sc.*, **1951**, *233*: 1059-1061.

ALBE-FESSARD, D. et HESSE, D. Le facteur de pression artérielle dans l'accroissement adrénalinique de l'activité corticale chez le lapin. *J. Physiol.*, **1953**, *45*: 16-20.

ALLEN, W. F. Formation reticularis and reticulo spinal tracts, their visceral functions and possible relationships to tonicity and chronic contractions. *J. Washington Acad. Sc.*, **1932**, *22*: 490-495.

ARDUINI, A. e LAIRY-BOUNES, G. C. Effetti della stimulazione della sostenza reticolare del bulbo e di stimoli sensoriali sulle onde strichniche corticali nel gatto ''encefale isolato''. *Boll. Soc. It. Biol. Sp.*, **1951**, *27*: 1634-1635.

ARDUINI, A., LAIRY-BOUNES, G. C., PARMA, M. e ZANCHETTI, A. L'attivita convulsiva prodotta dell'applicazione locale di stricnina sulla corteccia cerebrale del coniglio e le sue modificazione durante la reazione d'arreste di Berger. *Boll. Soc. It. Biol. Sp.*, **1951**, *27*: 1635-1636.

ARDUINI, A. et LAIRY-BOUNES, G. C. Action de la stimulation électrique de la formation réticulaire du bulbe et des stimulations sensorielles sur les ondes strychniques corticales chez le chat "encéphale isolé". *EEG Clin. Neurophysiol.*, **1952**, *4*: 503-512.

BACH, L. M. N. The role of the bulbar facilitory and inhibitory systems in vasomotor and respiratory activity. *Fed. Proc.*, **1948**, *7*.

BAILEY, P. and BREMER, F. A sensory cortical representation of the vague nerve (with a note on the effects of low blood pressure on the cortical electrogramme). *J. Neurophysiol.*, **1938**, *1*: 405-412.

BAISSET, BUGNARD, L., FISCHGOLD, H., GREZES-REUFF et PLANQUES. Ischémie cérébrale et épilepsie. *Ann. Med. Psychol.*, **1946**, *104*: 269-270.

BALDACCI, G. Vagotonia e epilessia riflessa nel cane. *Arch. Fisiol.*, **1937**, *37*: 566-584.

BARKER, W. Studies in epilepsy. Personality pattern, situational stress and the symptom of narcolepsy. *Psychosomat. Med.*, **1948**, *10*: 193-202.

BASTIANI, G. e PIOTTI, O. Alterazione cardiovasculari indotte dall'elettroschock nel cane. *Arch. Sc. Biol.*, **1949**, *33*: 489-502.

BATINI, C., PARMA, M., RICCI, G. F. e ZANCHETTI, A. Aspetti elettroencefalografici della sindrome convulsiva iperossica. *Arch. di Fisiol.*, **1953**, *53*: 346-353.

BATINI, C., PARMA, M., RICCI, G. F. e ZANCHETTI, A. Meccanismi piramidali ed extrapiramidali delle convulsioni iperossiche. *Arch. di Fisiol.*, **1953**, *53*: 362-369.

BELLA-BELLA, D. Caractères et nature des modifications de la pression artérielle au cours de l'électrochoc. *Arch. Int. Physiol.*, **1954**, *62*: 234-247.

BONVALLET, M., DELL, P. et HIEBEL, G. Tonus sympathique et activité électrique corticale. *EEG Clin. Neurophysiol.*, **1954**, *6*: 119-144.

BROWN, M. L., BROWN, G. W. and HINES, H. M. Cardiovascular and respiratory changes associated with electro-convulsive shock. *Amer. J. Physiol.*, **1951**, *167*: 771-772.

BROWN, M. L., BROWN, G. W. and HINES, H. M. Changes in blood flow, blood pressure and cardiac rate associated with electro-convulsive shock. *Amer. J. Psychiat.*, **1952**, *109*: 27-31.

DANIELOPOLU, M. Sur la pathogénie de l'épilepsie et sur son traitement chirurgical. *Presse Méd.*, **1933**, *41*: 170-174.

DANIELOPOLU, M., RADOVICI, A. et ASLAN, A. Mécanisme de la production des accès convulsifs provoqués chez l'homme par l'excitation du sinus carotidien. *Rev. Neurol.*, **1932**, *1*: 1326-1329.

DANIELOPOLU, M., RADOVICI, A. et MARCU, I. Influx de la zone réflexogène cardio-aortique sur l'écorce cérébrale. *Rev. Neurol.*, **1931**, *2*: 810-815.

DARROW, C. W., PATHMANN, J. and KRONENBERG, G. Level of autonomic activity and electro-encephalogramme. *J. Exper. Psychol.*, **1946**, *36*: 355-365.

DELAY, J. Syndrome humoral de l'électrochoc et réaction d'alarme de Selye. *Presse Méd.*, **1951**, *59*: 741.

DELAY, J., PARROT, J. L. et LUQUET. Electrochoc et régulation de la tension artérielle. *C. R. Soc. Biol.*, **1944**, *138*: 155-158.

DELAY, J., PARROT, J. L. et LUQUET. La crise tensionnelle de l'épilepsie électrique. *Ann. Médico-Psychol.*, **1944**, *1*: 290-293.

DELMAS-MARSALET, P. *Electrochoc thérapeutique et la dissolution - reconstruction.* Paris-Baillière, **1943**.

DELMAS-MARSALET, P., FAURE et ARNE. Hypertension artérielle et travail cardiaque dans l'électrochoc. *Paris Méd.*, **1945**, 53.

ELIASON, S., LINDGREN, P. and UVNAS, B. Representation in the hypothalamus and the motor cortex in the dog of the sympathetic vasodilatator outflow to the skelettal muscles. *Acta Physiol. Scand.*, **1952**, *27*: 18-37.

ERICKSON, TH. C. Spread of epileptic discharge. *Arch. Neurol. Psychiat.*, Chicago, **1940**, *43*: 429-452.

FABRICANT, J. The role of adrenaline in epilepsy. *Epilepsia*, **1954**, *3*: 126-134.

FAETH, W. H., EARL-WALKER, A. and ANDY, O. J. The propagation of cortical and subcortical epileptic discharge. *Epilepsia*, **1954**, *3*: 37-48.

FRANÇOIS-FRANCK, C. A. et PITRES. Recherches expérimentales sur les convulsions épileptiformes d'origine corticale. *Arch. Physiol.*, **1883**, *12*:101-144 et **1885**, *1*: 149-185.

FRANÇOIS-FRANCK, C. A. *Leçons sur les fonctions motrices du Cerveau.* Paris, Doin, **1887**.

FREEDMAN, D. A. and MOOSSY, J. Effect of mesencephalic lesions on the cortical electro-convulsivant threshold. *Neurology*, **1953**, *3*: 714-720.

FRENCH, J., HERNÁNDEZ-PEÓN, R. and LIVINGSTON, R. B. Projections from cortex to cephalic brainstem (reticular formations) in monkey. *J. Neurophysiol.*, **1955**, *18*: 74-95.

FRENCH, J., VERZEANO, M. and MAGOUN, H. W. A neural basis of the anesthetic state. *Arch. Neurol. Psychiat.*, Chicago, **1953**, *69*: 519.

GAYET, R., GAYET, TH. et GUILLAUMIE, M. Actions vasomotrices de l'adrénaline sur les muscles. Processus périphérique vaso-constricteur et processus central vaso-dilatateur. *C. R. Soc. Biol.*, **1927**, *97*: 1145-1147.

GELLHORN, E. The hypothalamic cortical system in barbiturate anesthesia. *Arch. Int. Pharmac.*, **1953**, *93*: 434-442.

GELLHORN, E. Subcortical centers as pacemakers of cortical activity. *Proc. Soc. Exp. Biol. Med.*, **1949**, *70*: 107-108.

GELLHORN, E. and BALLIN, H. Role of afferent impulses in experimental convulsions. *Arch. Neurol. Psychiat.*, Chicago, **1948**, *59*: 718-733.

GELLHORN, E., BALLIN, H. and RIGGLE, C. M. Hypothalamus and thalamus as pacemakers of cortical activity in asphyxia and anoxia. *Acta Neurovegetativa*, **1951**, *2*: 237.

GELLHORN, E. and BALLIN, H. Further investigations on effect of anoxia on convulsions. *Amer. J. Physiol.*, **1950**, *162*: 503-506.

GELLHORN, E. and DARROW, C. W. The action of Metrazol on the autonomic nervous system. *Arch. Int. Pharm. Ther.*, **1939**, *62*: 114-128.

GELLHORN, E., DARROW, C. W. and YESINICK, L. Effect of epinephrin on convulsions. *Arch. Neurol. Psychiat.*, Chicago, **1939**, *42*: 826.

GELLHORN, E., HYDE, J. and GAY, J. Proprioception and convulsion. *Arch. Int. Pharmacod.*, **1949**, *80*: 110-118.

GELLHORN, E., YESINICK, L., KESSLER, M. and HAILMAN, H. Carotid sinus reflexes and convulsions. *Amer. J. Physiol.*, **1942**, *137*: 396-403.

GIBBS, F. A. Cerebral blood flox preceding and accompanying experimental convulsions. *Arch. Neurol. Psychiat.*, Chicago, **1933**, *30*: 1003-1010.

GOLDSTEIN, L. et MINZ, B. Effets d'un déséquilibre hormonal sur la sensibilité corticale et vasculaire à l'adrénaline. *C. R. Soc. Biol.*, **1954**, *148*: 1007-1009.

GOLDSTEIN, L. et MINZ, B. L'action de l'adrénaline sur l'activité corticale du lapin normal. Utilisation d'une méthode nouvelle d'évaluation des données corticographiques. *J. Physiol.*, **1955**, *47*: 180-181.

GREDER, G. *Syndrome neuro-végétatif dans l'épilepsie expérimentale.* Thèse Médecine, Genève, **1952.**

GREEN, J. D. and MORIN, F. Hypothalamic electrical activity and hypothalamo cortical relationships. *Amer. J. Physiol.*, **1953**, *172*: 175-186.

GUTIÉRREZ-NORIEGA, C. y ROTONDO, H. Reacciones neuro-vegetativas en la epilepsia experimental. *Rev. Neuropsiquiat.*, Lima, **1939**, *2*: 185-227.

HALL, G. E. and LEIBEL, B. Physiological studies in experimental insulin and Metrazol shock. V. Effect of autonomic drugs on Metrazol convulsions. *Amer. J. Psychiat.*, **1938**, *95*: 553-566.

VAN HARREVELD, A. and STAMM, J. S. Spreading cortical convulsions and depressions. *J. Neurophysiol.*, **1953**, *16*: 352-366.

HERNÁNDEZ-PEÓN, R. and HAGBARTH, K. E. Interaction between afferent and cortically induced reticular responses. *J. Neurophysiol.*, **1955**, *18*: 44-55.

HESS, W. R. *Vegetativen funktionen und zwicheuhirn schwabe.* Bâle, **1946.**

HEYMANS, C. et BOUCKAERT, J. J. Au sujet de l'influence des zones vasosensibles réflexogènes du sinus carotidien et de l'aorte sur l'excitabilité corticale motrice. *Presse Méd.*, **1933**, *41*: 729-730.

HIEBEL, G., BONVALLET, M. et DELL, P. Action de la chlorpromazine (Largactil, 4560 RP) au niveau du système nerveux central. *Sem. Hôp.*, Paris, **1954**, *30*: 2346-2353.

HOEFFER, P. F. A. and POOT, M. J. L. Conduction of cortical impulses and motor management of convulsives seizures. *Arch. Neurol. Psychiat.*, Chicago, **1943**, *50*: 381-400.

INGVAR, D. H. Extraneuronal influences upon the electrical activity of isolated cortex following stimulation of the reticular activating system. *Acta Physiol. Scand.*, **1955**, *33*: 169-193.

JASPER, H. H., AJMONE-MARSAN, C. and STOLL, J. Experimental studies of the subcortical projections of local cortical epileptiform discharge. *Trans. Amer. Neurol. Ass.*, **1951**, *76*: 3.

JASPER, H. H., AJMONE-MARSAN, C. and STOLL, J. Cortico-fugal projections to the brain stem. *Arch. Neurol. Psychiat.*, Chicago, **1952**, *67*: 155-171.

KAADA, B. R. Somatomotor, autonomic and electrocorticographic responses to electrical stimulation of rhinencephalic and other structures in primates, cat and dog. *Acta Physiol. Scand.*, **1951**, *23*: Supp. p. 83 sqq.

KABAT, H., MAGOUN, H. W. and RANSON, S. W. Electrical stimulation of points in the forebrain and midbrain; the resultant alterations in blood pressure. *Arch. Neurol. Psychiat.*, Chicago, **1935**, *34*: 931-955.

KOCH, E. Die irradiation der pressorezeptorischen Kreislaufreflexe. *Klin. Wschr.*, **1932**, *11*: 225-227.

KOPELOFF, L. M., BARRERA, S. E. and KOPELOFF, H. Recurrent convulsive seizures in animals produced by immunologic and chemical means. *Amer. J. Psychiat.*, **1942**, *98*: 881-902.

KOPELOFF, N., KENNARD, M. A., PACELLA, B. L., KOPELOFF, L. M. and CHUSID, J. C. Section of corpus callosum in experimental epilepsy in the monkey. *Arch. Neurol. Psychiat.*, Chicago, **1950**, *63*: 719-727.

KREINDLER, A. Recherches expérimentales sur les réactions entre le sinus carotidien et le système nerveux central. *Bull. Sc. Scient. Acad.*, Roumanie, **1946**, *28*: 448-481.

KURZIUS, H. and HANN, J. Blood adrenaline in electroshock. *Deutsch. Zeitschf. Nervenheilk.*, **1951**, *165*: 80-89.

LAFON, R., PASSOUANT, P. et MINVIELLE, J. Action de l'infiltration péricarotidienne de novocaïne sur l'aptitude convulsivante du cerveau. Etude clinique et électroencéphalographique. *Ve Congrès Neurol. Int.*, Lisbonne, **1953** et voir également *Rev. Neurol.*, **1953**, *89*: 519.

LAIRY-BOUNES, G. C., PARMA, M. et ZANCHETTI, A. Modifications pendant la réaction d'arrêt de Berger de l'activité convulsive produite par l'application locale de strychnine sur le cortex cérébral du lapin. *EEG Clin. Neurophysiol.*, **1952**, *4*: 495-502.

LEIBEL, B. and HALL, G. E. Cerebral blood flow changes during schock therapy. *Amer. J. Psychiat.*, **1938**, *95*: 555-557.

MAGOUN, H. W. Recent contributions to seizure activation. *Epilepsia*, **1952**, *1*: 69-82.

MARTINO, G. Sull'azione del chloralosio sull'epilessia sperimentale da eccitamente afferenti nel cane. *Arch. di Fisiol.*, **1931**, *29*: 412-424.

MARTINO, G. Sulla partecipazione delle zone riflessogene dell'aorta e dei seni caroditei al fenomeno dell'epilessia sperimentale riflessa. *Arch. di Fisiol.*, **1934**, *33*: 598-603.

MASSION-VERNIORY, L., DUMONT, E., NICAISE, R. et REINHOLD, H. Les variations de la pression artérielle au cours de l'électrochoc sous curare. *J. belge Neurol. Psychiat.*, **1947**, *47*: 624.

MINZ, B. et CHAMORRO, A. Sur une action cortico-hypothalamique déclenchée par l'adrénaline. *C. R. Acad. Sc.*, Paris, 24 Janvier **1955**, *C. R. Soc. Biol.*, **1955**, *149*: 309.

MINZ, B., ALBE-FESSARD, D. et BUSER, P. A propos de l'épilepsie corticale provoquée chez le lapin thyréoprivé chronique. *J. Physiol.*, **1951**, *43*: 815-816.

MINZ, B., BUSER, P. et ALBE-FESSARD, D. Effet presseur de l'adrénaline appliquée localement sur le cortex du lapin. *C. R. Soc. Biol.*, **1953**, *147*: 1154-1156.

MINZ, B. and DOMINO, F. Effects of epinephrine and norepinephrine on electrically induced seizures. *J. Pharmacol. Exp. Therap.*, **1953**, *107*: 204-218.

MINZ, B. and KING, E. E. Epinephrine modification of the effects of brain stem stimulation on the patellar and linguo-mendibular reflexes. *J. Pharmacol. Exp. Therap.*, **1952**, *106*: 407-409.

MINZ, B., RÉMOND, A. G. and MCCULLOCH, W. S. Local effects of epinephrine on the cerebral cortex. *Proc. Soc. Exp. Biol. Med.*, **1953**, *83*: 306-308.

MINZ, B., VELLEY, G. C. et GOLDSTEIN, L. Action de broyats de surrénale sur le corticogramme du lapin. *C. R. Soc. Biol.*, **1954**, *148*: 498-500.

MOLINELLI, E. *La secreción de adrenalina.* Thèse, Buenos-Aires, **1926.**

MORUZZI, G. Il risveglio della corteccia cerebrale. *Medicina* (Parma) **1952**, *5*: 577-596.

MORUZZI, G. and MAGOUN, H. W. Brain stem reticular formation and activation of EEG. *EEG Clin. Neurophysiol.*, **1949**, *1*: 455-473.

MURPHY, J. P. and GELLHORN, E. The influence of hypothalamic stimulation on corticaly induced movement and action potentials of the cortex. *J. Neurophysiol.*, **1945**, *8*: 339-364.

MURPHY, J. P. and GELLHORN, E. Further investigations on diencephalic cortical relations and their significance for the problem of emotion. *J. Neurophysiol.*, **1945**, *8*: 431-447.

NIEMER, W. T. and JIMÉNEZ-CASTELLANOS, J. Corticothalamic connections in the cat as revealed by physiological neuronography. *J. Comp. Neurol.*, **1950**, *93*: 101-123.

PARMA, M., RICCI, G. F. e ZANCHETTI, A. Componenti piramidali ed estrapiramidali del clono strinico e dell'epilessia faradica. *Arch. di Fisiol.*, Firenze, **1953**, *53*: 354-361.

PARMA, M., RICCI, G. F. e ZANCHETTI, A. Modificazioni del clono strinico e dell'epilessia da intense stimolazioni elettriche per lesioni piramidali ed estrapiramidali. *Boll. Soc. It. Biol. Sper.*, **1953**, *29*: 1381-1382.

PIETTE, X. Motor, respiratory, cardiovascular and blood-sugar changes during electric shock. *Amer. Soc. Roy. Sc. Med. and Nat.*, Bruxelles, **1950**, *5*: 71.

PORTER, R. W. Alterations on the electrical activity of the hypothalamus induced by stress stimuli. *Amer. J. Physiol.*, **1952**, *169*: 629-637.

PORTER, R. W. Hypothalamic involvement in the pituitary-adrenocortical response to stress stimuli. *Amer. J. Physiol.*, **1953**, *172*: 514-519.

RADOUCO, C., FROMMEL, ED., GOLD, PH., GREDER, G., MELKONIAN, D., RADOUCO, S., STRASSBERGER, L., VALETTE, F. et DUCOMMUN, M. Etude physiopathologique de l'action du pentaméthylène-tétrazol (Cardiazol). *Arch. Int. Pharmacod.*, **1952**, *92*: 13-38.

RADOUCO, C., FROMMEL, ED., GOLD, PH., GREDER, G., MELKONIAN, D., RADOUCO, S., STRASSBERGER, L., VALETTE, F. et DUCOMMUN, M. La physiologie de l'épilepsie électrique expérimentale. *Arch. Int. Pharmacod.*, **1952**, *92*: 129-162.

REINERS, H. und WATTEROTT, A. Die Bedentung der Schilddrüse in der genese epileptiformer Krampfzustände. *Ztsch. ges. exp. med.*, **1938**, *103*: 750-755.

RUF, H. Experimentelle Untersynchungen über Krampfverlängerung durch Sauerstoff und Adrenalin: Dauerkrmmpfe nach einmaliger elektrischer Reizung oder Cardiazolgabe. *Arch. Psychiat. Neurol.*, Chicago, **1951**, *187*: 97-127.

SCHEIER, F. *La physiologie de l'électrocrise.* Thèse Médecine, Genève, **1951**.

SCHMITERLOW, C. G. and SILFVERSKIOLD, B. P. Disturbance of circulation in convulsion of epileptic type. Animal experiment. *Acta Physiol. Scand.*, **1943**, *6*: 187.

SCHOETENSACK, W. und HANN, J. Zur Wirkkung der Narcotica auf die Blutzucker regulation und zur Differenzierung swischen Schlaf und Narcose (nach Metersuchungen leim Electrokramps). *Arch. exp. Path. Pharm.*, **1951**, *213*: 102-110.

STOLL, J., AJMONE-MARSAN, C. and JASPER, H. H. Electrophysiological studies of subcortical connections of anterior temporal region in cat. *J. Neurophysiol.*, **1951**, *14*: 305-316.

TANAKA, K. and KAN, N. The mechanism of pressor and depressor responses to electrically induced convulsion. *Jap. J. Pharmacol.*, **1952**, *2*: 1-2.

TERZIAN, H. e TERZUOLO, C. Ricerche elettrofisiologiche sull'epilessia di Clementi nel coniglio. *Boll. Soc. Ital. Biol. Sper.*, **1950**, *26*: 1243-1244.

TOURNADE, A., RAYNAUD, R. et CHARDON, G. L'hypertension de la crise d'épilepsie expérimentale procède, pour une part, d'une décharge d'adrénaline. *C. R. Soc. Biol.*, **1939**, *130*: 632-634.

TOURNADE, A. et MALMEJAC, J. Diversité des actions réflexes que déclenche l'excitation du sinus carotidien et de son nerf. *C. R. Soc. Biol.*, **1929**, *100*: 708-711.

TOURNADE, A. et MALMEJAC, J. De l'action vasodilatatrice centrale de l'adrénaline. *C. R. Soc. Biol.*, **1933**, *113*: 163-166.

TOURNADE, A. et MALMEJAC, J. Des effets vasodilatateurs qui engendrent au niveau de la circulation périphérique (musculaire et rénale) l'action strictement centrale de l'adrénaline. *C. R. Soc. Biol.*, **1933**, *114*: 1247-1250.

WARD, A. A., JR. and MCCULLOCH, W. S. The projections of the frontal lobe on the hypothalamus. *J. Neurophysiol.*, **1946**, *9*: 329-335.

ZANCHETTI, A., WANG, S. C. and MORUZZI, G. The effect of vagal afferent stimulation on the EEG pattern of the cat. *EEG Clin. Neurophysiol.*, **1952**, *4*: 357-361.

Reference: MORIN, G. et CORRIOL, J. Les variations de la pression artérielle provoquées par les crises d'épilepsie. *EEG Clin. Neurophysiol.*, **1957**, *9*: 59-82.

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STUDIES OF CEREBRAL CIRCULATION IN BRAIN INJURY

IV. — Ischemia and Hypoxemia of the Brain Stem and Respiratory Center [1]

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INTRODUCTION

Experimental observations concerning the respiratory effects of occlusion of the cerebral vessels have been studied since the early work of Cooper (1836), Pagano (1900), Hill (1900) and Siciliano (1900). Occlusion of the carotid arteries in the neck produces a temporary hyperpnea, occlusion of the carotid and vertebral arteries together causes respiratory slowing, failure and death.

While engaged in studies of the mechanisms of adjustment in the collateral circulation following experimental brain trauma and ischemia (Meyer and Denny-Brown 1954, 1955) we became interested in the striking effects of ischemia and hypoxemia of the brain stem.

As the respiratory center is an aggregate of neurones whose functional state can be recorded continually with a pneumograph a detailed study of the respiratory effects of cerebral ischemia, hypoxemia and hypercapnea is reported here. The respirations, blood pressure, oxygen availability (EPG) of the carotid body together with the pH, oxygen availability (EPG) and steady potential (SP) of the respiratory center were recorded concurrently. Correlation of such data allows analysis of the effects of anoxic damage to the neurones of the respiratory center in terms of function, rhythmicity, survival and revival times and relation of these to any local injury potential (SP shift). In addition we have been able to record metabolic effects of nerve cell injury and resulting circulatory effects.

The method of study used in these experiments permits recording of the series of events that go on during respiratory stimulation and depression by changes in the oxygen tension of the carotid body and respiratory center. We have assumed that the fixed base in the blood remains constant over intervals of a few seconds and that any rapid changes that are measured in pH of the respiratory center will reflect either changes in the CO_2 tension of the blood or local acidity in the center due to the production of acid metabolites (Gesell 1925).

METHODS

In this series of experiments observations have been made on 17 cats and 7 monkeys (Macacus mulatta). The results obtained were not different in the two species.

Records were made of the local oxygen availability of the cerebrum, cerebellum, brain stem, respiratory center and carotid body concurrently by the modification of the polarographic method described by us in previous stndies (Meyer, Fang and Denny-Brown 1954; Meyer and Denny-Brown 1955). A silver-silver chloride anode was used which was freshly coated with silver chloride for each experiment. For the active electrode (cathode) we have used the exposed tips of platinum wires. In some experiments Teflon insulation was used which is more durable than Tygon insulation. Insulating of the electrodes with Teflon was done commercially by the Grass Instrument Company, Quincy, Massachusetts. The exposed area of platinum was 1-2 mm. and made as uniform as possible so that when calibrated before each experiment the electrodes gave comparable readings in saline at different oxygen tensions.

The principle of the polarographic method requires a potential of 0.6 V. supplied to the anode by

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Opinions expressed are those of the author and do not necessarily represent those of the Department of the Navy.

a potentiometer. The platinum electrode is connected to the positive pole of the potentiometer through a resistance of 1.2 million ohms. On either side of this resistance leads are then taken to the input of a vacuum tube microammeter. In this way calibration in electrical units is possible. For recording on bromide paper we have used a galvanometer connected to the external output of the microammeter.

For recording oxygen availability in the region of the carotid body, the external carotid and occipital artery were exposed by dissection and the tip of the electrode was inserted through the wall of the carotid artery into the intima as close to the carotid body at the origin of the occipital artery as possible. In some experiments the electrode tip was found at necropsy to have penetrated partially through the intima of the vessel and to be lying in the flow of arterial blood. Heparin was used to prevent clotting. The insulated wire of the electrode was then held in place by suturing it to the carotid sheath.

Placement of the electrodes in the respiratory center was made following the anatomical description of the medullary inspiratory and expiratory centers by Pitts and associates (Pitts, Magoun and Ranson 1939; Pitts 1946). The electrodes were placed dorsally through the medulla after suboccipital craniectomy and exposing the brain stem and cerebellum. Occasionally, the cervical spinal cord was also exposed by cervical laminectomy. Any exposed brain or brain stem was covered with a thin layer of warm mineral oil. The position of the electrodes was later verified microscopically after making serial sections of the medulla and staining them with luxol fast blue counterstained with cresyl violet.

Concurrent records of local blood flow of spinal cord, cerebellum, brain and brain stem were also made in terms of local changes in temperature measured with microthermistor beads mounted on glass probes ground to a fine point as described by us in a previous communication (Meyer *et al.* 1955).

The direct current or steady potential (SP) of the respiratory center were recorded with paired silver-silver chloride electrodes (showing a potential difference of less than 10 mV.) and millivoltmeter (Meyer *et al.* 1955). The active electrode was inserted into the respiratory center and the reference electrode was placed in the white matter of the spinal cord.

Femoral blood pressure was recorded with a Statham Strain Gage and a polyethylene catheter, in some experiments the intracranial pressure was recorded with a modified strain gage screwed into the skull (Meyer and Denny-Brown 1955). Respirations were recorded with a trochar placed in the intrapleural space connected to a Marey Tambour reflecting a light image on the camera lens. In the records inspiration is recorded as an upward deflection and expiration as a downward deflection.

In some experiments the concurrent EEG and EKG was recorded with a Grass III-D electroencephalograph.

Anesthesia in all experiments has been light pentobarbital anesthesia in doses of 0.4 to 0.6 g. per kilogram of body weight. Tracheotomy was routinely performed. The tracheal cannula was connected to a three way glass tube so that gaseous content of the inspired air could be rapidly changed. The common carotid arteries were dissected free of their sheath in the neck and ligatures were passed around them and through a polyethylene tube. In this way the carotid arteries were not displaced when occluded by gentle traction on the ligatures. To test the effect of occlusion of the vertebral arteries digital compression was applied to the neck between the lateral processes of the first and second cervical vertebras.

RESULTS

General observations.

It was found that the types of electrode used in these experiments could be inserted into the respiratory center without disturbing its functional integrity. An EPG electrode placed in the respiratory center, upper brain stem, spinal cord or cerebellum records a similar pattern of changes to an EPG electrode of equal sensitivity recording concurrently from the cortex when 100 per cent nitrogen or 7 per cent oxygen is breathed after air. The oxygen availability of the brain stem remains constant if the animal is lightly anesthetized and immobile. Small fluctuations occur when an arousal response is elicited in the lightly anesthetized animal.

An EPG electrode placed in the intima of the carotid artery appears to give a faithful record of changes in the partial pressure of the plasma oxygen. When a 10 per cent mixture of carbon monoxide and air (coal gas) is breathed after oxygen the EPG oxygen of the carotid blood near the carotid body gives a brief fall while the gas is being administered and rises promptly to resting levels when oxygen breathing is resumed (fig. 1 C). The oxygen availability of the respiratory center shows a continued fall for several minutes after the carotid blood EPG oxygen has returned to baseline reflecting the lowered effective oxygen carrying capacity of the blood because of the formation of carbon monoxy-

hemoglobin. The formation of carbon monoxy-hemoglobin does not affect the plasma oxygen content. Presumably the respirations are only temporarily slowed because the oxygen dissolved in the plasma may provide a critical level of oxygen sufficient to maintain the viability of the respiratory center (Haldane 1927).

the oxygen availability of the respiratory center decreases (fig. 2). With nitrogen breathing, a similar latency between the fall of the arterial oxygen saturation measured by the ear oximeter and the oxygen availability of the cerebral cortex has been reported previously (Meyer and Denny-Brown 1955). The brief latency indicates that the respiratory

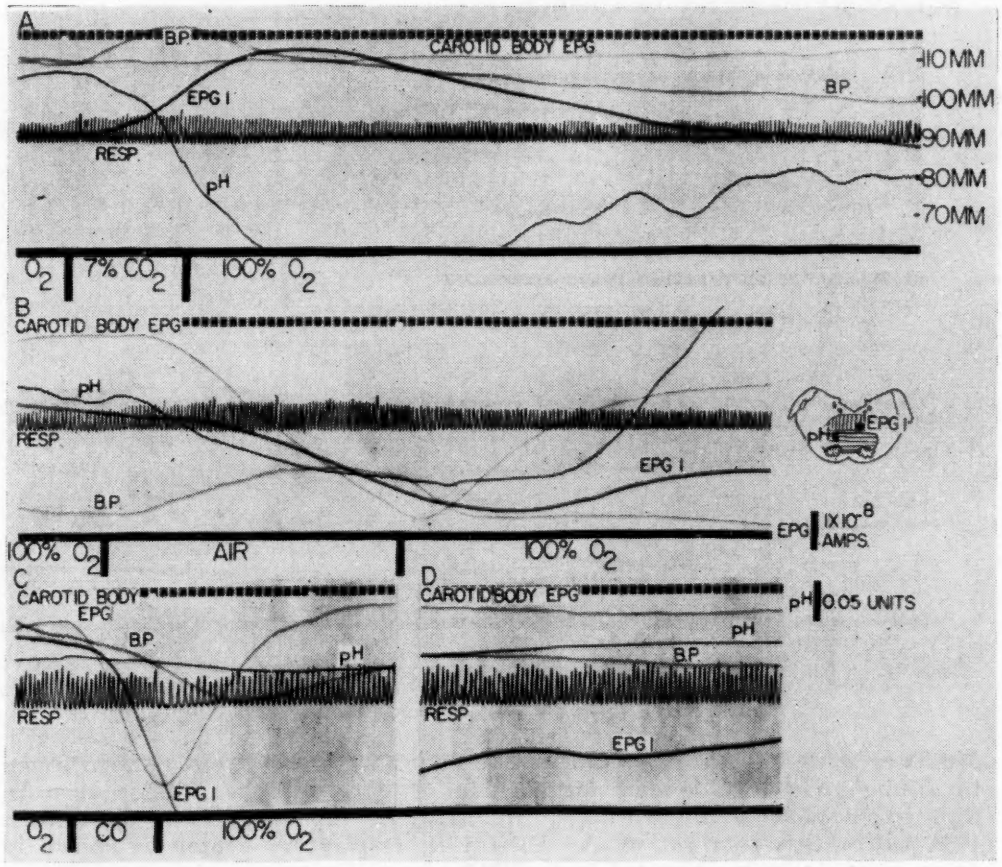

Fig. 1

Monkey. Examples of respiratory effects of changes in the composition of the inspired air (see text). Four records, same experiment as figure 4. Light Nembutal anesthesia. B.P. calibration to right of B. Position of EPG and pH electrodes in respiratory center shown in brain stem diagram. Carotid body EPG placed in the carotid artery near carotid body. In A, 7 per cent CO_2 and 93 per cent oxygen mixture is breathed instead of 100 per cent oxygen. In B air (20 per cent oxygen mixture) is breathed instead of 100 per cent oxygen. In C, 10 per cent carbon monoxide (coal gas) is breathed after oxygen. D shows recovery phase 2½ min. later. EPG = polarograph electrode, B.P. = femoral blood pressure. Resp. = respirations, time intervals at top of each record indicate 6 sec. intervals. Calibration of EPG electrodes same for all. Initial reading of EPG 1 in A = 10×10^{-8} A., of carotid body EPG = 27×10^{-8} A.

One hundred per cent nitrogen breathing produces a steep fall in the oxygen availability of the carotid blood since both the plasma and hemoglobin are rapidly deoxygenated. Nitrogen breathing causes a prompt fall in blood oxygen availability, 4 sec. after the carotid blood EPG oxygen begins to decline

center, like the cortex, has no significant reserve of tissue oxygen. Resumption of air or oxygen breathing after nitrogen results in a prompt rise in the carotid arterial oxygen availability (fig. 2 A) providing the respiratory center has not been damaged in which case the rise may be delayed (fig. 2 B, C and

3 B). The oxygen availability of the respiratory center lags behind the recovery of the arterial blood reoxygenation. It may continue to fall or level off for several seconds or minutes before rising. The latency of the rise in the oxygen availability of the center with the resumption of air or oxygen breathing after nitrogen varies according to the severity of the hypoxemia. The latency appears to depend on the rapidity of the rise in the reoxygenation of the blood, the level of the blood pressure and the degree of local vasodilatation in the respiratory center. If the supply of oxygen brought by a deficient circulation to the center is slow then the metabolic demands of the respiratory center keep pace with the supply. Rarely a comparable situation is seen in the cortex after ischemic anoxia (fig. 4 A, B). If oxygen is breathed, prior to nitrogen the initial oxygen availability of tissue and blood plasma is higher and hence there is a slightly longer latency before the oxygen availability of the respiratory center approaches zero and respirations fails.

When temporary respiratory arrest is induced by nitrogen breathing, substitution of air for nitrogen results in a small increase in carotid blood EPG oxygen before respiration returns (fig. 3 B) and presumably reflects the simple diffusion of oxygen across pulmonary capillaries.

If temporary arrest occurs from neuronal hypoxic paralysis the neurones continue to metabolize oxygen since the EPG oxygen of the respiratory center may remain at or near zero for as long as 1-6 min. after carotid blood oxygen has started to rise (fig. 5 B, C, D). Such hypoxic neuronal paralysis is associated with a localised reduction in pH which may amount to 0.3 pH units. While this acidity

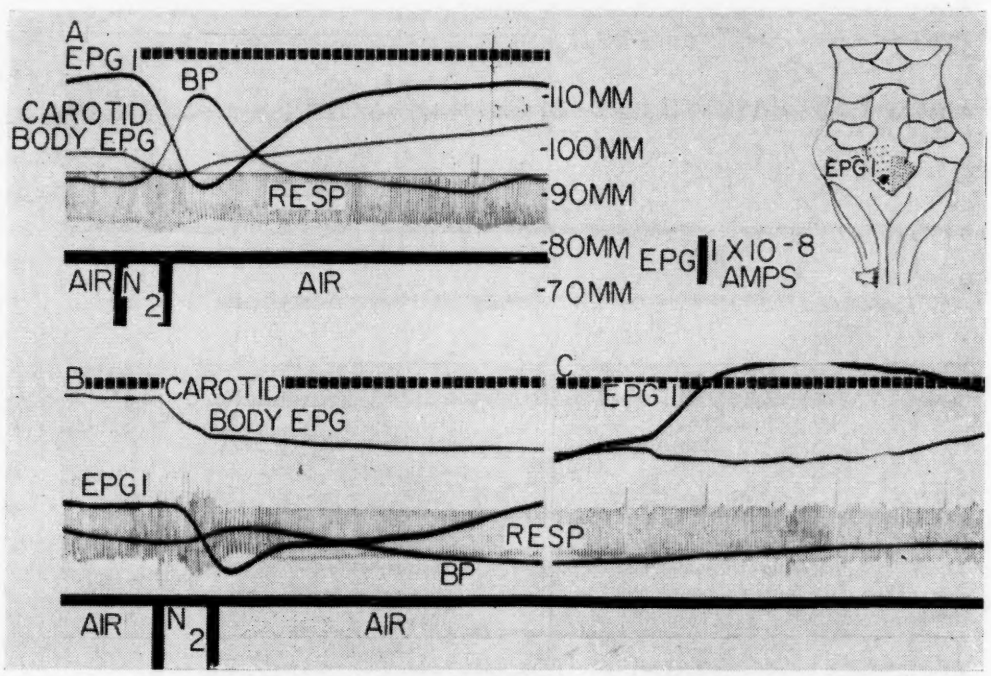

Fig. 2

Monkey. A and B are two examples of reflex hyperpnea following nitrogen breathing caused by anoxic stimulation of carotid body. Three records, same experiment. C continues 2½ min. after B. Light Nembutal anesthesia. B.P. calibration to right of A. EPG 1 in respiratory center as shown in brain-stem diagram. Carotid body EPG placed in intima of carotid artery near carotid body. Note differences in latency of changes in oxygen availability between carotid body and respiratory center. When respiratory center becomes anoxic respiration slows. In the recovery phase, C, note marked reactive hyperemia which occurs due to anoxic damage to respiratory center.
EPG = polarograph electrode, B.P. = femoral blood pressure, Resp. = respirations. Time intervals at top of record indicate 6 sec.
Initial reading of EPG 1 in A = 8×10^{-8} A.
Initial reading in carotid body EPG in A = 20×10^{-8} A.

of injury is rapid in development (occurring over a period of 1-4 min.) it is slow in resolving and may take 7-15 min. or longer to return to the baseline pH reading. Lesser, rapid fluctuations in pH are seen with changes in CO_2 tension of the blood. Small fluctuations of pH also occur with brief carbon monoxide breathing or changing from pure oxygen to air breathing (fig. 1 B, C).

Anoxic or ischemic damage to the respiratory center sufficient to cause arrest or irregularity of the respirations consistently results in a marked supernormal phase of local oxygen availability (fig. 2 C, 8 B). The reactive period may be associated with an increase of oxygen availability of the respiratory center by as much as 40 per cent. This hyperoxic phase, as in cerebral cortex, is in marked contrast to white matter and indicates that the respiratory center is very vascular, comparable to the cerebral cortex. The reactive rise of local oxygen availability may be unaccompanied by any change in the respiratory rhythm or rise in the oxygen availability of the carotid blood, but is accompanied by an increase in temperature. It appears to be a reactive hyperemia of the type described in the cerebral cortex (Meyer, Fang and Denny-Brown 1954).

Effects of Vascular Occlusion.

Carotid Arteries.

Occlusion of one or both carotid arteries while the animal is breathing air results in an increase in rate and depth of respirations. Hyperventilation usually begins after 6 sec. and is maximal after 18-24 sec. (fig. 4 A, B). The phenomenon can be abolished by breathing pure oxygen (fig. 4 C, D). It has been reported to be abolished by denervation of the carotid sinuses in the dog (Heymans *et al.* 1930). In the cat if the nerve supply to the

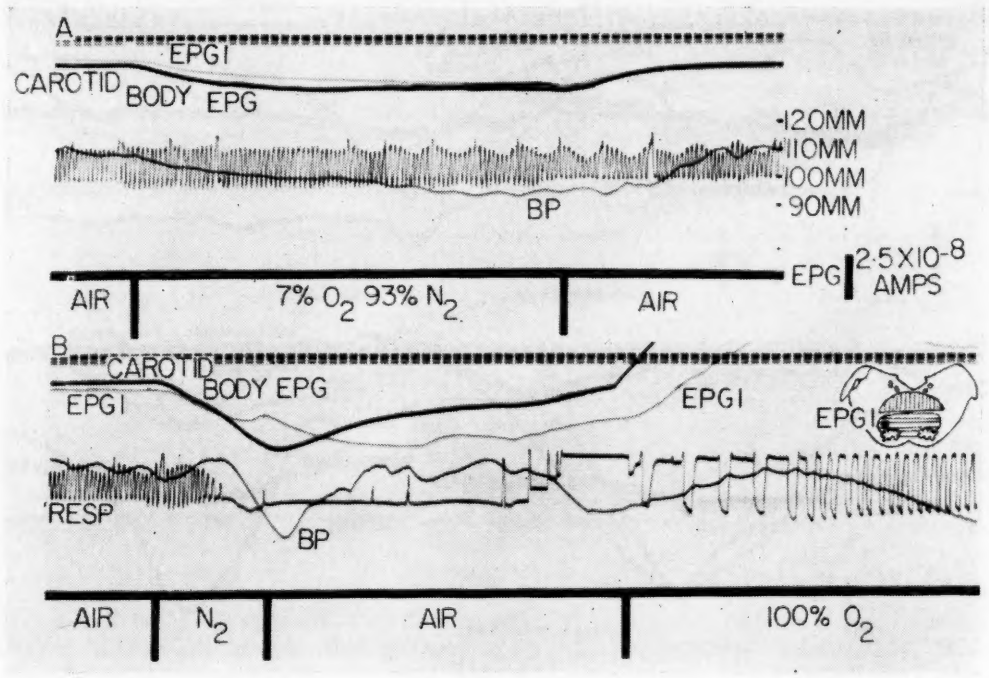

Fig. 3

Cat. Two examples of abnormal respiratory patterns following anoxemia of the respiratory center. Two records same experiment. *B. continuous from A. Light Nembutal anesthesia. B.P. calibration to right of A. EPG in respiratory center as shown in brain-stem near carotid body. In A, a mixture of 7 per cent oxygen and 93 per cent nitrogen was breathed resulting in waxing and waning of respirations and Traube-Herring waves in the blood pressure. In B, 100 per cent nitrogen breathing causes respiratory arrest due to anoxia of the respiratory center, followed by apneusis.

EPG = polarograph electrode, B.P. = femoral blood pressure, Resp. = respiration. Time intervals at top of record indicate 6 sec.

Initial reading of EPG 1 in A = 6.5×10^{-8} A.

Initial reading of carotid body EPG in A = 20×10^{-8} A.

carotid bodies is preserved and the carotid sinus alone is denervated, carotid occlusion under the conditions of our experiments still results in some degree of hyperventilation (fig. 9 A). In general, our evidence indicates that the hyperpnea caused by carotid occlusion in the cat and monkey is primarily due to hypoxic stimulation of the carotid body, rather than the carotid sinus baroreceptor reflex. The latter mechanism causes respiratory stimulation when a fall in carotid blood pressure takes place (Heymans and Boucaert 1930). It seems unlikely that this factor is of major importance in the hyperventilation of carotid occlusion since the response may be abolished by oxygen breathing which does not alter the fall in carotid blood pressure.

In the series of experiments reported here occlusion of a carotid artery in the neck causes a slow gradient of fall in the oxygen availability of the carotid body distal to the point of occlusion. When the animal is breathing air the hyperpnea corresponds closely to the fall in the carotid body EPG oxygen. Breathing oxygen prior to occlusion of the carotid artery results in a much higher initial EPG oxygen level and abolishes the response (fig. 8 A). The fall in the carotid body EPG oxygen following carotid occlusion has a slow gradient of development similar to that associated with the development of hyperpnea. Any fall in intraluminal pressure of the carotid artery is rapid and reaches a maximum within 3 or 4 sec. (Sweet and Bennet 1948). The slower fall of carotid body EPG oxygen caused by occlusion of the common carotid artery is presumed to be to a continued tissue demand of the carotid body itself.

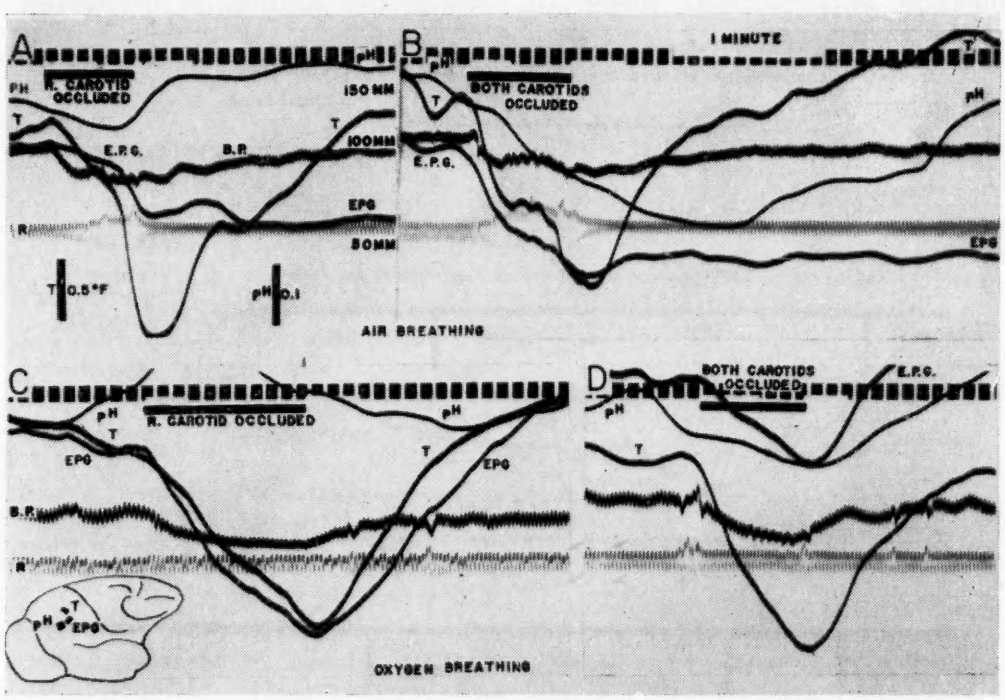

Fig. 4

Monkey. A and B are examples of hyperpnea produced by unilateral or bilateral carotid occlusion. C and D are examples of abolition of this response when animal is breathing 100 per cent oxygen. Four records same experiment. Light Nembutal anesthesia. Electrode positions shown on brain diagram. EPG baseline lowered after oxygen breathing between B and C. T = temperature electrode, EPG = polarograph electrode, pH = pH electrode, B.P. = femoral blood pressure. Time intervals indicate 6 sec.

The reflex hyperpnea produced by occlusion of one or both carotid arteries is clearly not due to central hypoxia or acidity. Occlusion of either one or both carotid arteries results in a rise in the oxygen availability of the respiratory center (fig. 6 A), and an alkaline change in its pH. These changes in oxygen availability and pH are directly related to an increase in the collateral circulation arising from the vertebral, basilar and dorsal spinal arterial system (fig. 6 A, 7 B,

9 D). The increased collateral circulation concerns not only the basilar artery flow but also the tissue supplied by it.

This increased blood flow of the hind brain closely follows the fall in local oxygen availability and temperature of the forebrain. The cortical oxygen availability in the distribution of supply of the carotid arteries continues to fall as the hind brain oxygen availability rises (fig. 7 A, B). After 40-60 sec. the hyperemia of the brain stem is at a maximum and is accompanied by hyperemia of the occipital cortex which has been shown to provide the collateral circulation for the Sylvian region when one carotid artery is occluded (Meyer, Fang and Denny-Brown 1954). Under favorable circumstances brain stem hyperemia, following brief carotid occlusion, begins within 8 sec., reaches a maximum within a minute and subsides within 2 min. after the flow in the carotid artery has been restored. If carotid occlusion has been prolonged, hyper-

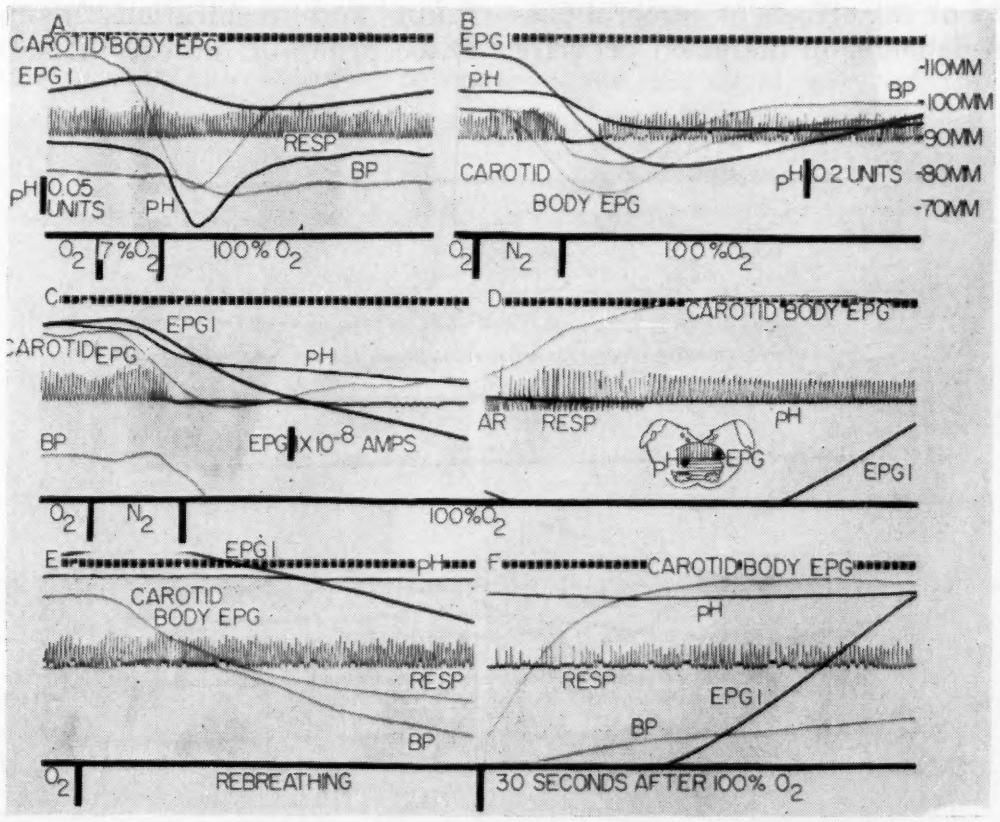

Fig. 5

Monkey. Examples of different degrees of anoxemia of the respiratory center and consequent changes in respiratory rhythm (see text). Six records, same experiment. D continues 2½ min. after C. F continues 4½ min. after E. Light Nembutal anesthesia. B.P. calibration to right of B. Position of pH and EPG electrodes in respiratory center shown in brain stem diagram. Carotid body EPG placed in intima of carotid artery near carotid body. In A, waxing and waning of respiration results from repeated brief inhalation of 7 per cent oxygen and 93 per cent nitrogen mixture. In B, respiratory arrest is produced by 100 per cent nitrogen breathing with waxing, waning and ataxia of respirations. In C prolonged respiratory arrest when 100 per cent nitrogen breathing is repeated. D shows gasping respirations in recovery phase. E and F show ataxic respirations following progressive anoxia caused by rebreathing into a balloon.
EPG = polarograph electrode, B.P. = femoral blood pressure, Resp. = respirations. Time intervals at top of record indicate 6 sec. Calibration of EPG electrodes same for all; pH calibration changed at B. A.R. = artificial respiration.
Initial reading EPG 1 in A and E = 10×10^{-8} A., in B and C 8×10^{-8} Amp.
Initial reading carotid body EPG = 27×10^{-8} A.

emia subsides more slowly. The hyperemia following occlusion of one carotid artery is less than that following bilateral carotid occlusion and has a lesser gradient of rise. The dorsal spinal arteries contribute to this hyperemia of the brain stem (fig. 7 B).

The severity of the effects of cerebral vascular occlusion depends on the blood pressure and oxygen tension of the blood (Meyer, Fang and Denny-Brown 1954; Meyer and Denny-Brown 1955). Figure 7 shows the relation of these factors to respiratory function. Initially the oxygen tension of the arterial blood in figure 7 A is high following prolonged oxygen breathing. Under such circumstances carotid occlusion has no effect on respirations. When the arterial oxygen tension is lowered by breathing 7 per cent oxygen carotid occlusion now produces severe cerebral anoxemia resulting in respiratory slowing (fig. 7 A). In figure 7 B, occlusion of both carotid arteries when the blood pressure and tissue oxygen are low results in critical anoxia of the entire brain and respirations temporarily cease. Disocclusion of the carotid arteries results in resumption of respiration. One hundred per cent oxygen breathing only partially restores the EPG oxygen levels in the tissues because the blood pressure remains low and occlusion of the carotid arteries under these conditions causes first a slight stimulation of respiration and then respiratory slowing without respiratory arrest. In this experiment, seven per cent oxygen breathing when the blood pres-

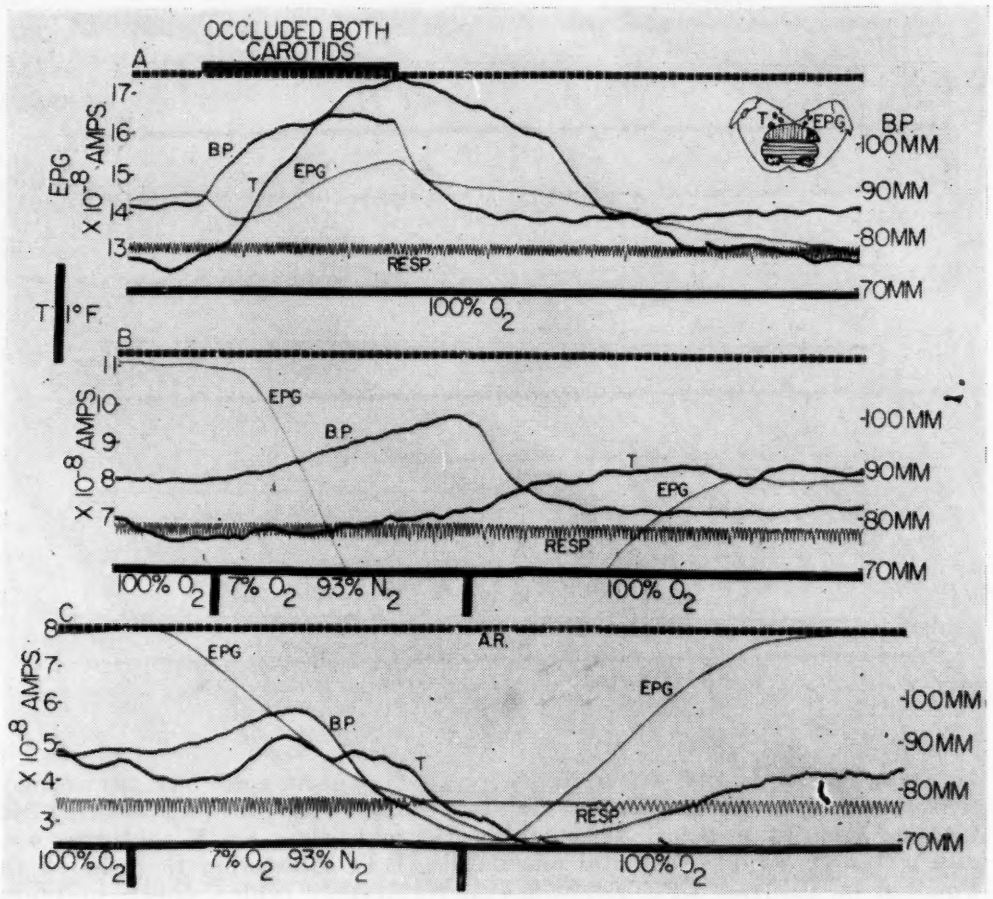

Fig. 6

Cat. To show effect of bilateral carotid occlusion and of repeated anoxemia of respiratory center (see text) produced by breathing a mixture of 7 per cent oxygen and 93 per cent nitrogen. Light Nembutal anesthesia. B.P. calibration to right of each record. EPG and temperature (T) electrodes in respiratory center as shown in brain stem diagram. EPG calibration to left of each record.
EPG = polarograph electrode (light line), T = temperature electrode (dark line) Resp. = respiration. Time intervals at top of record indicate 6 sec.

sure is low results in Cheyne-Stokes respiration. Normal respirations are resumed when air is breathed.

Vertebral Arteries. Occlusion of the vertebral arteries results in a fall in the oxygen availability of the respiratory center, brain stem and the occipital cortex (fig. 8 B, 9 B, C). The fall in EPG oxygen is greater in the brain stem than it is in the occipital cortex (fig. 8 B). In spite of this, the EEG of the occipital cortex shows localized high voltage delta at a time when the respirations show no irregularity, suggesting that the neurones of the respiratory center have a greater resistance to ischemic anoxia than the occipital cortex.

The first respiratory effect of vertebral artery occlusion is a transient stimulation of respiration followed by irregularity and occasionally respiratory failure (fig. 7 B, 8 B, 9 B, C). The respiratory changes are due to direct ischemic anoxia of the respiratory center itself since carotid body blood flow is unchanged or increased and there is an accompanying rise in blood pressure. When the carotid arteries are occluded in addition to the vertebral arteries the oxygen availability of the respiratory center falls nearly to zero and respirations cease (fig. 8 B). When all four vessels are released the oxygen availability of the respiratory center promptly rises and respirations are rapidly resumed. Both cortex and medulla show the effects of a marked hyperemia greater in the respiratory center which had been rendered more ischemic.

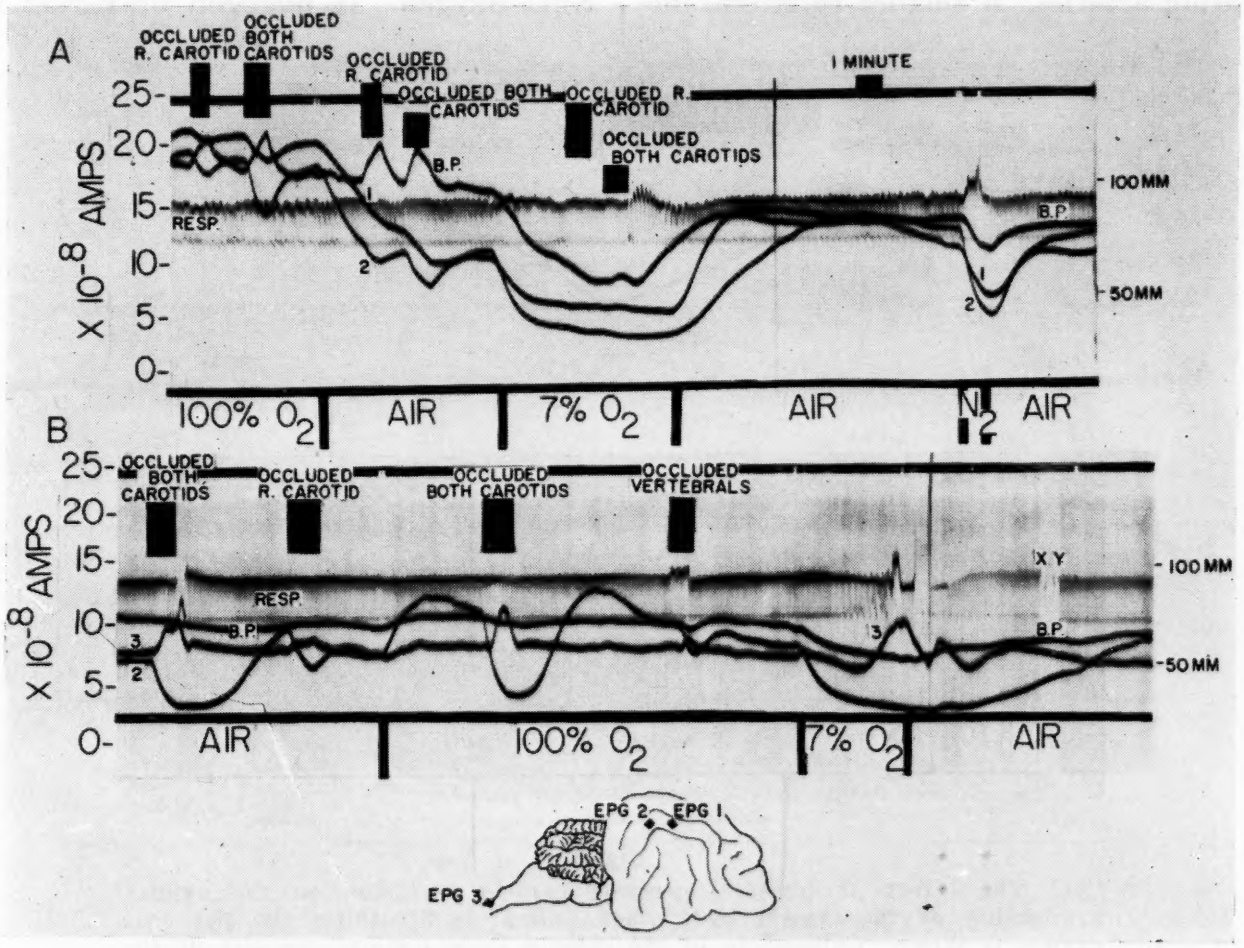

Fig. 7

Cat. To show effects of carotid and vertebral artery occlusion with animal breathing different concentrations of oxygen (see text). One EPG electrode is in cortex in A (EPG 1) and in spinal cord in B (EPG 3). The other electrode (EPG 2) was not moved from cortex. Two slow-speed records, same experiment. In B, 7 per cent oxygen breathing produced Cheyne-Stokes respiration. EPG electrode positions shown in diagram of brain. Blood pressure calibration to right of records, EPG calibration to left of record.
EPG = polarograph electrode, B.P. = femoral blood pressure, Resp. = respiration. Black interval marked "1 MINUTE" at top of record A indicates 1 min.

The fact that the oxygen availability of the respiratory center falls nearly to zero when the carotid arteries are occluded, secondary to occlusion of the vertebral arteries, gives a definite clue to the blood supply of the respiratory center during the emergency produced by vertebral artery occlusion. The major collateral circulation appears to be from the carotid arteries via the posterior communicating arteries. A smaller collateral circulation is also provided by the spinal arteries (fig. 7 B).

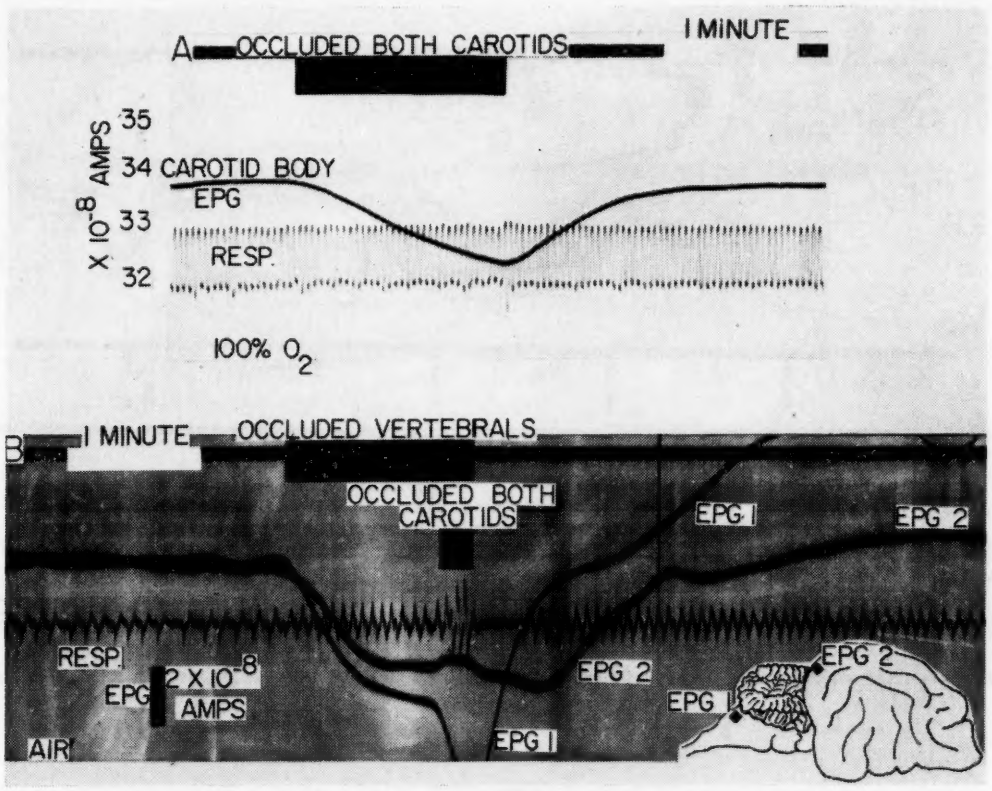

Fig. 8

Cat. The effect of bilateral common carotid occlusion on the oxygen availability of the carotid body when animal is breathing 100 per cent oxygen is shown. Calibration of the carotid body EPG to the left of the record. There is no hyperpnea (see text). B. The effect of occluding first both vertebral and then both carotid arteries in the cat. EPG 1 in respiratory center, EPG 2 in occipital cortex (see diagram). Light Nembutal anesthesia.
Resp. = respiration, EPG = polarograph electrode. Time interval indicated at top of record by white block.

Changes in the composition of the inspired gas. Nitrogen.

The first respiratory effect of 100 per cent nitrogen breathing is a fall in the carotid body EPG oxygen resulting in an increase in rate and an increase in depth of respiration (fig. 2 A). In the vagotomized, carotid sinus denervated preparation with preservation of the carotid body hyperpnea occurs after a delay of 12 sec. (fig. 9 A). In the non-vagotomized preparation respirations are faster and deeper and respiratory stimulation occurs after a shorter delay of 8 sec. corresponding closely with the fall in EPG oxygen of the carotid body (fig. 2 A, B). Hyperventilation is usually well established before the respiratory center shows a fall in EPG oxygen. If nitrogen breathing is continued, respiration is slowed presumably due to anoxic damage of the respiratory center, since it develops as the EPG oxygen in the respiratory center approaches zero. If air breathing is immediately restored the respirations will increase in rate to a normal rhythm, as the anoxia of the respiratory center subsides. The briefer the anoxia of the respiratory center the more rapidly respirations resume their normal rhythm (fig. 2 A, B). If the hypoxia of the respiratory center is pre-

sent for 45 sec. or longer the electrode changes associated with marked reactive hyperemia appear (fig. 2 B, C). More prolonged nitrogen breathing, particularly if the blood pressure falls, results in severe hypoxia of the respiratory center. The gradient of tissue oxygen deprivation seems important in relation to neuronal damage for nitrogen breathing results in respiratory arrest more rapidly than (fig. 7 B, 10 A). These abnormal respiratory patterns, under the conditions of these experiments are not found to be associated with any rhythmic changes in pH or oxygen availability of carotid body (fig. 1 C, D; 5 A, B, C, D, E, F; 3 A). Apneustic breathing is occasionally seen as a transient phenomenon following severe cerebral anoxia (fig. 3 B). Occasionally it may persist for one or two

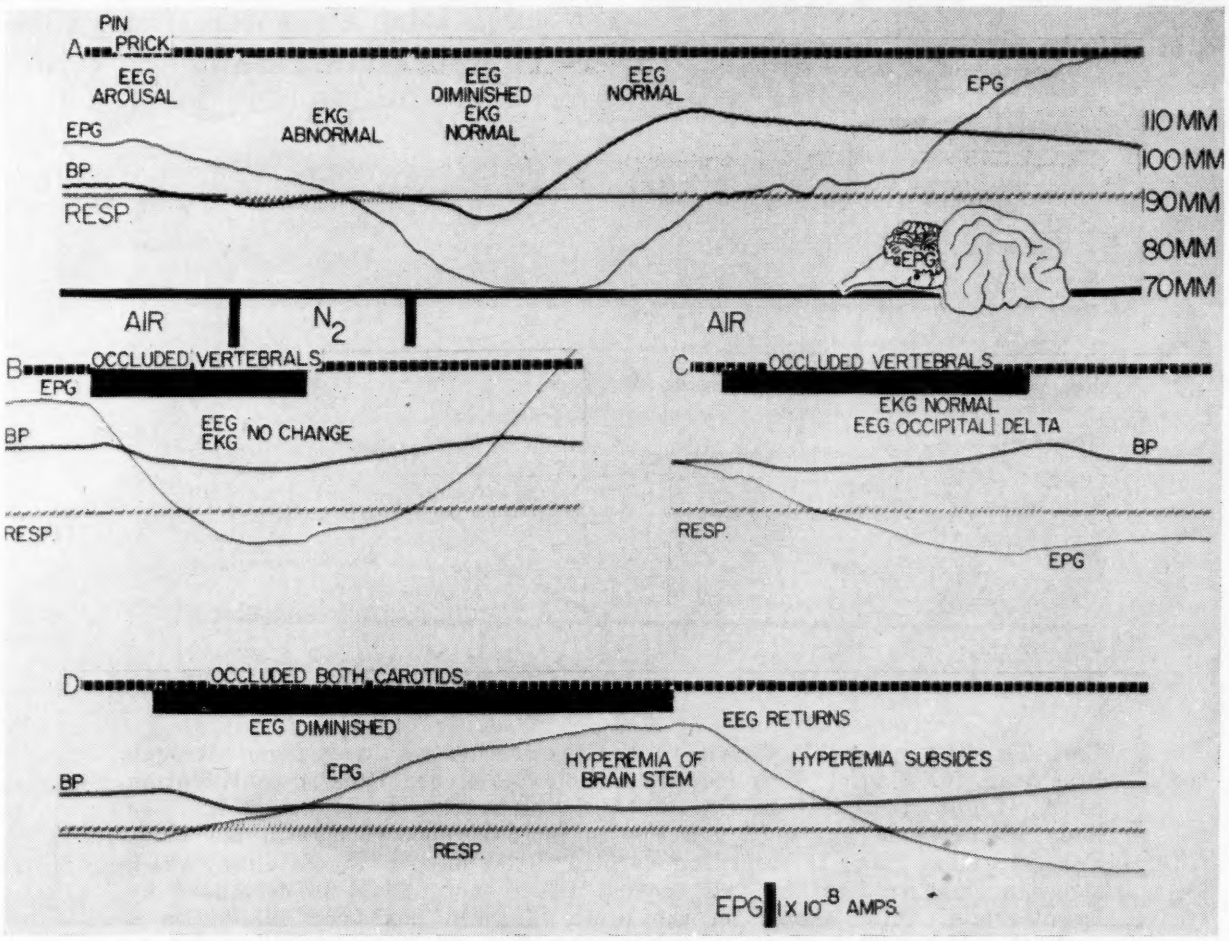

Fig. 9

Cat. To compare effect of 100 per cent nitrogen breathing, occlusion of vertebral arteries and occlusion of carotid arteries (see text). Four records, same experiment. Light Nembutal anesthesia. BP calibration to right of record A. EPG in reticular substance of pons as shown in diagram. Concurrent EEG and EKG changes are noted on record. Animal vagotomized, carotid sinus denervated, carotid body intact.
EPG = polarograph electrode, B.P. = femoral blood pressure, Resp. = respirations. Time intervals at top of record indicate 6 sec.

breathing a mixture of 7 per cent oxygen and 93 per cent nitrogen. The more steep the fall the more severe the respiratory effects.

After repeated brief episodes of anoxia various patterns of abnormal respiration may result. Waxing and waning of respiration is common (fig. 1 C, D; 3 A, B; 5 A, B, C, D, E). This frequently becomes ataxic (fig. 5 B, F) and rarely Cheyne-Stokes in character hours, but death from respiratory failure almost invariably ensues. Gasping respirations are sometimes seen as a result of severe prolonged anoxia of the respiratory center (fig. 11 A, B). They may be reversible, but respiration following them is slow suggesting damage to the respiratory center. Very slow respirations function poorly, and further exposure to anoxia is likely to cause complete

failure. Blood and tissue EPG oxygen levels are usually low. Damage to the respiratory center renders it prone to repeated anoxia which tends to be rapidly fatal.

If respiratory arrest occurs from hypoxic or ischemic paralysis of the respiratory center it shows an injury potential (SP shift) of 4-10 mV. negative with respect to spinal cord white matter. The SP shift coincides with the development of slow gasping respirations mains stable during hyperventilation from any physiological cause. It is only when respirations cease or become gasping in character that the respiratory center develops an injury potential. When 100 per cent nitrogen is breathed during hypothermia the gradient of fall in oxygen availability of carotid blood and respiratory center is less steep than in the warm state due to decreased tissue utilization of oxygen. The nerve cells continue to

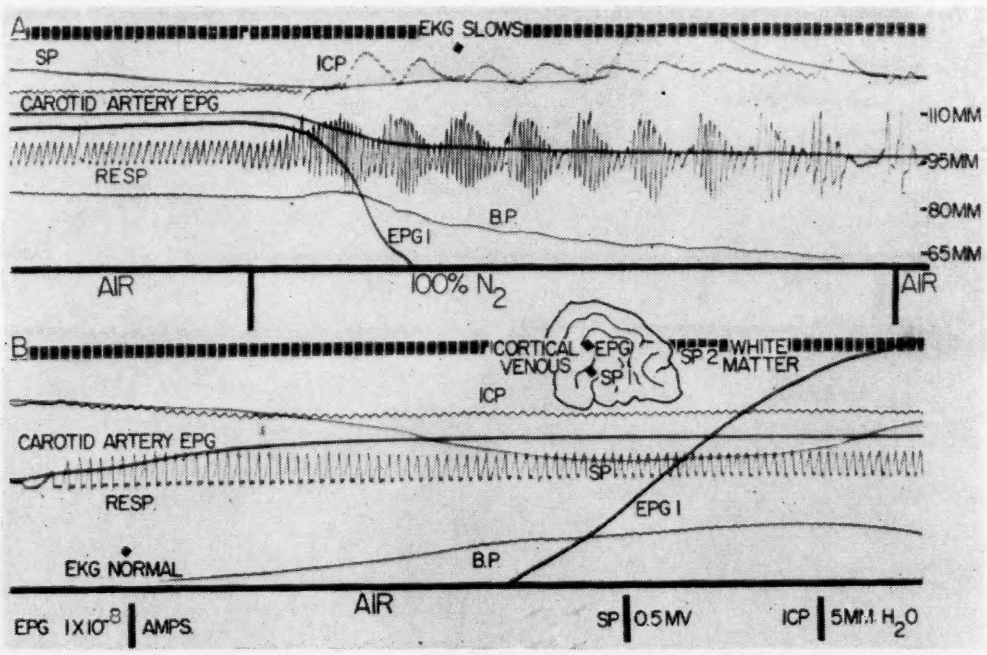

Fig. 10

Cat. To show reversible Cheyne-Stokes respiration resulting from nitrogen breathing for 6 min. Two records same experiment. B is a continuation of A. Light Nembutal anesthesia. B.P. calibration to right of A. The body temperature has been lowered to 25.5 degrees C. by an ice bath. Carotid artery EPG is recording carotid blood oxygen availability, which shows a slow gradient of fall because tissue metabolism is decreased by hypothermia. EPG shown on the brain diagram has been placed on a cortical vein. S.P. records an injury potential of cortex with respect to subcortical white matter. Intracranial pressure (ICP) shows fluctuations which are dependent on the intrathoracic pressure. As the cerebral venous EPG oxygen availability decreases Cheyne-Stokes respiration begin, as it rises normal respiration results (see text). Anesthesia Nembutal and chlorpromazine (5 mg.). Concurrent EKG changes are noted on the record. Initial carotid artery EPG reading 25 $\times$ 10^{-8} Amp. Initial cortical venous EPG reading 15 $\times$ 10^{-8} A.

(fig. 11 A) and returns to baseline as normal respiratory rhythm returns (fig. 11 A). If respiration fails irreversibly the SP change continues as a permanent injury potential (fig. 11 A, B). During Cheyne-Stokes respiration the cortex shows an injury potential with respect to subcortical white matter, but it does not appear to correlate with the abnormal respiratory rhythm (fig. 10). The steady potential of the respiratory center remetabolize oxygen but at a reduced rate (fig. 10). An investigation of the effects of hypothermia will be discussed in detail in a later publication (Meyer and Hunter 1957).

Seven per cent oxygen.

When a mixture of 7 per cent oxygen and 93 per cent nitrogen is breathed the gradient of fall in oxygen availability of blood and respiratory center is less steep than when

100 per cent nitrogen is breathed. The first effect is hyperpnea due to stimulation of the carotid body (fig. 3 A; 5 A; 6 B, C; 7 A, B). The second effect is respiratory slowing and occasionally arrest due to medullary anoxia (fig. 6 B, C; 7). Anoxia of the respiratory center is accompanied by a compensatory vasodilatation and the temperature of the center rises (fig. 6 B). The local hyperemia is due to an increased blood flow from the bordering vessels such as the dorsal spinal vessels (fig. 7 B). If anoxia of the brain stem results in a failure of blood pressure the local vasodilatation in the center fails (indicated by a fall in its temperature) and respiration fails due to local neuronal anoxic paralysis (fig. 6 C).

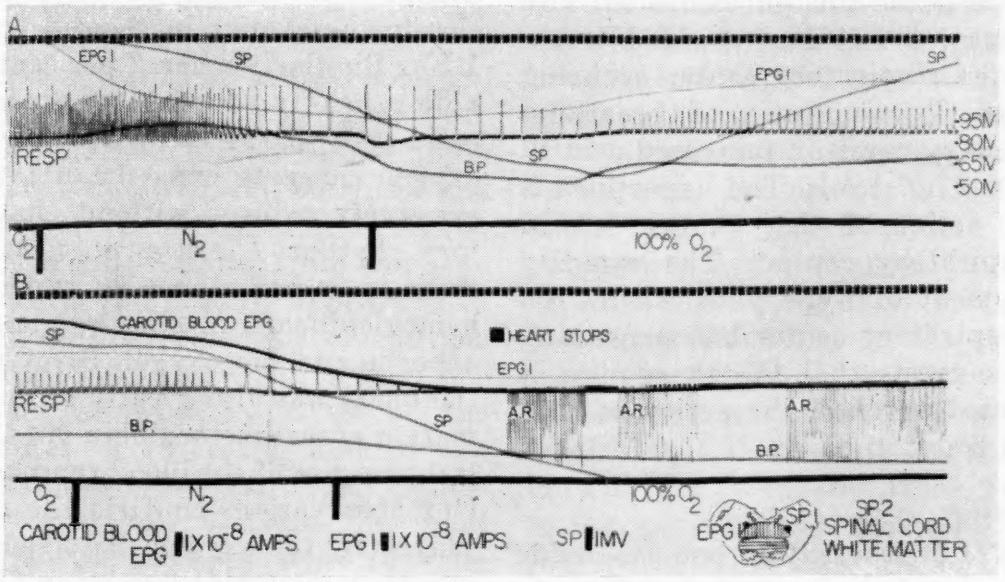

Fig. 11

Monkey. A. To show reversible damage to respiratory center with gasping respirations and injury potential (SP) due to anoxia of center following 100 per cent nitrogen breathing. B. Repeat 100 per cent nitrogen breathing causes death due to irreversible damage to respiratory center. Two records same experiment. B. continues 2 min. after A. Light Nembutal anesthesia. Blood pressure calibration to right of A. EPG = polarograph electrode, SP = steady potential (D.C.) electrode recording injury potential, BP = femoral blood pressure. Position of EPG 1 and SP 1 in respiratory center shown in diagram. SP 2 is recording from spinal cord white matter. Carotid blood EPG was inserted into the carotid artery near the carotid body. AR = artificial respiration. In A the carotid blood EPG oxygen showed a decrease with nitrogen breathing and a rise with oxygen breathing which was not recorded on the camera. The initial oxygen availability of the carotid blood was at low levels in B due to a fall in blood pressure but exact figures are not available. Initial reading of EPG 1 = 6×10^{-8} A.

Rebreathing.

Asphyxia, by rebreathing into a small balloon without CO_2 absorption, so that the pneumograph tracing can be recorded, results in a slowly progressive reduction in the oxygen availability of both blood and respiratory center (fig. 5 E, F). The blood pressure eventually falls. In figure 5 E the pH shows a less rapid and severe acidity than when asphyxia is caused by tracheal obstruction (Meyer and Denny-Brown 1955). As the EPG oxygen of the respiratory center slowly

Oxygen breathing.

One hundred per cent oxygen breathing results in shallow, slow respirations (fig. 1 B; 4, 7). When air is breathed after 100 per cent

approaches zero the respiration becomes first waxing and waning and then ataxic. Oxygen breathing restored the oxygen availability of the respiratory center and normal respirations (fig. 5 F).

Carbon Dioxide.

The addition of 7 per cent CO_2 to a mixture of air or oxygen results in marked and consistent hyperpnea (fig. 1 A). Respiration is increased in rate and depth. The oxygen availability of the carotid body is unchanged while that of the respiratory center rises due to local vasodilatation and an associated rise in blood pressure. There is a rapid decrease in the pH of the respiratory center occuring after 8-12 sec. Two minutes of breathing 7 per cent CO_2 may result in increased acidity of 0.3 pH units (fig. 1 A). The hyperpnea is clearly due to action of CO_2 on the carotid body and respiratory center. The rapidity of the development of hyperpnea within 4-6 sec. (before respiratory center has shown any acid change) suggests that the hyperpnea is initially mediated through the action of CO_2 on the carotid body.

Carbon Monoxide.

A mixture of 2 per cent carbon monoxide added to the inspired air does not significantly effect the carotid body EPG oxygen and respirations are not stimulated. The formation of carbon monoxyhemoglobin like methhemoglobin progressively reduces the oxygen carrying capacity of the blood in spite of a normal partial pressure of arterial oxygen. Hence the blood EPG oxygen remains unchanged while the oxygen availability in the respiratory center falls reflecting the diminished oxygen carrying capacity of the blood. As the arterial oxygen carrying capacity is reduced, neuronal demand exceeds supply for the oxygen supply is mainly that dissolved in the plasma. Inhalation of higher concentrations of carbon monoxide such as commercial coal gas (fig. 1 C) causes a transient fall in the carotid body EPG oxygen only while the gas is being administered. When 10 per cent oxygen is again breathed the oxygen dissolved in the plasma is sufficient to restore normal respirations, but the EPG in the respiratory center remains at low levels for several minutes since oxygen supply is barely meeting tissue demand (fig. 1 D).

DISCUSSION

The polarograph electrode inserted into the wall of the carotid artery near the carotid body reflects changes in the oxygen tension of the blood plasma and not the saturation of the blood. In this way a relatively large fall occurs in the blood oxygen availability when air is breathed after oxygen while the oxygen saturation of the blood changes relatively little. The hyperpnea accompanying the change from oxygen to air breathing follows closely the change in carotid body EPG (fig. 1 B). Similarly when 2 per cent carbon monoxide is briefly added to an air mixture the carotid body shows no significant fall while the oxygen carrying capacity of the blood is progressively reduced without change in respiratory rhythm. Clark *et al.* (1943) found that there is no hyperpnea in experimental methhemoglobinemia produced by aniline. In their experiments the oxygen carrying capacity of the blood was also greatly reduced by the formation of methhemoglobin but the oxygen partial pressure of the blood remained unchanged. Our observations confirm the important part played by the oxygen dissolved in the plasma in carbon monoxide poisoning (Haldane 1927). Furthermore, the results reported here are consistent with the observations of Comroe and Schmidt (1938) that a decreased arterial oxygen content without a sufficient decrease in oxygen partial pressure is an inadequate stimulus for the carotid body reflex.

When the common carotid artery is occluded in the neck the plasma oxygen availability of the carotid body also falls. If the initial level is high (as in oxygen breathing) respiration is not stimulated; if it is at a low initial level, as when breathing air, the fall results in reflex hyperventilation.

Seven per cent CO_2 breathing produces a marked hyperventilation response which is due in its early phase to stimulation of the carotid body. Later effects may be due to the effects of CO_2 on the center since the pH of the medulla rapidly shows an acid change.

Injury to the respiratory center from ischemia or anoxia results in marked local acidity by as much as 0.3 pH units. This metabolic

acidity of the center is associated with respiratory depression.

Abnormal respiratory rhythms produced by brief anoxia such as apneustic and gasping breathing are similar to those produced by section of the brain stem at various levels (Hoff and Breckenridge 1955) except that they are more or less transient and are therefore assumed to be due to reversible paralysis at various levels of brain stem.

Repeated brief ischemia or anoxia of the brain stem tends to lower the threshold of the respiratory neurones to anoxic paralysis. For example, in figure 11 A the first administration of nitrogen for 3.8 min. produces gasping respirations and a transient injury potential of the respiratory center but the second administration of nitrogen for 3.2 min. rapidly produced an irreversible injury potential and permanent respiratory failure (fig. 11 A, B).

Respiratory arrest resulting from occlusion of vertebral and carotid arteries appears to be due to anoxic neuronal paralysis of the medullary respiratory center (fig. 8 B). The resulting anoxic neuronal paralysis of the respiratory center is reversible and of the same type as that produced by nitrogen breathing. Similar reversible ischemic neuronal paralysis of cerebrum has been shown to occur in man with severe insufficiency of the carotid and basilar arteries (Meyer, Leiderman and Denny-Brown 1956). How long this hypoxic neuronal paralysis remains reversible cannot be satisfactorily evaluated by the type of experiment reported here since prolonged respiratory failure itself results in further anoxic and circulatory complications. However, in this series of experiments transient anoxic paralysis of the respiratory center has persisted for 7 min. with recovery (fig. 5 C, D). The heart beat continued during this time although the blood pressure fell to 40 mmHg. Anoxemia was not absolute throughout this period as the EPG oxygen of the carotid blood was rising (fig. 5 C), presumably from diffusion in the quiescent lung. The respiratory center continues to metabolize oxygen during this period of paralysis since the local oxygen availability shows a slow gradient of decline.

In previous studies it has been shown that the early consequences of cortical ischemia are due to local hypoxic damage to neurones (Meyer, Fang and Denny-Brown 1954; Meyer and Denny-Brown 1955). Anoxia of the cerebral cortex results in two degrees of reversible nerve cell injury, the first change is reflected in the EEG as a slowing and change in potential occuring after 8 sec. of anoxia, the second change is the injury potential of SP shift occuring after 2 to 4 min. The only change in respiratory function within the first 10 sec. of anoxia is the hyperventilation response which is clearly reflex in nature. Sugar and Gerard (1938) reported that abrupt and complete cerebral anemia in the cat abolished the EEG potentials of the cortex in 14-15 sec. whereas it took 30-40 sec. to abolish the fast potentials of the medulla, however, slow potentials persisted for as long as 2-4 min. Respiratory arrest and the associated injury potential of the medullary respiratory center occurred in the experiments reported here after 2 to 4 min. of nitrogen breathing depending on the state of the systemic circulation. If anoxia is often repeated this latency is shorter. Available evidence indicates that if absolute anoxia is prolonged beyond 3½ min. the EEG activity of the cortex permanently disappears and the injury potential is irreversible (Ganshirt *et al.* 1954; Kempinsky 1954; Meyer and Denny-Brown 1955). Heymans (1938) has shown that the respiratory, cardioregulatory and vasomotor centers possess great resistance to anemic anoxia and can still be reversed in dogs after the circulation has been arrested completely for as long as 30 min. If the anoxia is not absolute, however, as in figure 5 C, the hypoxic neuronal paralysis may presumably persist for longer periods and remain reversible. The work of Ganshirt and associates (1952) indicates that reversible ischemic paralysis results in a reduction of the basal metabolic requirements necessary to maintain the viability of the damaged nerve cells by 80 per cent of that required for normal functional activity.

Clinical and electroencephalographic evidence in man indicates that ischemic neuronal paralysis may persist for days or weeks and still remain reversible providing the local circulation is restored (Meyer, Wegner and Kane 1957). The physiological basis of this

reversible state of neuronal paralysis has been discussed in another communication (Meyer, Leiderman and Denny-Brown 1956). The experiments reported here are of interest in relation to alterations in the neurogenesis of respiration. Whenever the oxygen availability of the medullary respiratory center approached zero levels respiration ceases within a few seconds and is accompanied by a local injury potential. Because the EPG electrode measures a gradient between oxygen supply and oxygen demand, and the threshold for anoxic damage is influenced by previous injury, respirations cease at various low points on the slope of oxygen availability as it levels off to a plateau near zero levels (fig. 3 B; 5 B, C; 6 C; 8 B; 11 A, B). EPG electrodes placed in brain, cerebellum, spinal cord and upper brain stem do not bear this close relationship to the arrest of respiration (fig. 7 A, B; 8 B; 9 A, B,C). The pattern of abnormal respiration resulting from brain stem ischemia and anoxia correspond to those predictable from the studies of Hoff and Breckenridge (1949, 1950, 1954) and confirm the regulatory nature of the neuronal hierarchy above the medulla (Gesell *et al.* 1946).

It is apparent from many of the experiments reported here that various abnormal respiratory patterns arise including Cheyne-Stokes, apneustic and ataxic breathing following anoxic damage to the brain as the medulla recovers (fig. 5 F; 7 A, B; 8 B).

They are more or less reversible depending on the severity of the anoxia. These abnormal respiratory patterns resulting under the conditions cited in these experiments are independent of any periodic changes in the oxygen availability or pH of arterial blood or respiratory center.

Periodic breathing.

Cheyne-Stokes breathing occurred rarely and unpredictably in this series of experiments (fig. 7 B, 10). It was rapidly reversible when it did occur. Waxing and waning of respirations without periodic apnea was more regularly produced. Both rhythms were the result of slowly progressive anoxic damage to the brain (fig. 1 C; 3 B; 5 A, B, C, E; 7 B). If the anoxic damage was continued ataxic, apneustic breathing or respiratory arrest would result (fig. 1 C; 3 B; 5 C, F; 11 B). Rarely waxing and waning respirations occurred with the shallow breathing caused by inhalation of 100 per cent oxygen (fig. 1 A) after the hyperventilation of 7 per cent CO_2 and oxygen. In this experiment slight rhythmical changes occurred in pH of the respiratory center synchronous with the waxing and waning of respiration but in all other experiments the periodic breathing was unaccompanied by periodic changes in oxygen availability or pH. Under the conditions of these experiments we would agree with the conclusions of Hoff and Breckenridge that periodicity of breathing may not always be a result of a reciprocation between the respiratory system and some other system such as the blood or cardiovascular system, but may be caused by damage to the intrinsic nervous regulation. Neurological observations in patients with expanding lesions of the brain suggest that in such conditions this is the commonest cause of periodic breathing.

SUMMARY

Concurrent studies of local blood flow, oxygen availability, steady potential (SP) and pH of the respiratory center and carotid body have been made together with continuous recording of blood pressure and respirations. The EPG electrode placed in the wall of the carotid artery records changes in the partial pressure of oxygen of the blood rather than changes in oxygen saturation.

The first effect of anoxic anoxia is stimulation of respiration by the carotid body reflex, continued anoxic anoxia or ischemic anoxia damages the respiratory center, resulting in various patterns of dysrhythmia such as slowed respiration, Cheyne-Stokes breathing, apneusis, gasping and finally respiratory arrest. Incomplete anoxia of the respiratory center causes respiratory arrest due to a state of reversible anoxic neuronal paralysis. In this state of reversible paralysis the respiratory neurones continue to metabolize oxigen but at a reduced rate. Anoxic damage to the respiratory center is associated with local acidity and hyperemia. Whenever respirations fail there is an accompanying injury potential (SP shift) of the respiratory center with respect to the spinal cord white matter.

Seven per cent CO_2 and oxygen causes hyperpnea which appears to be mediated in the first few seconds by its action on the carotid body and later by its additional action on the respiratory center.

Occlusion of the carotid arteries cause hyperpnea which is mainly due to resultant hypoxemia of the carotid body. There is an increased blood flow in the collateral circulation from the vertebral, basilar and dorsal spinal arteries. Occlusion of the vertebral arteries causes incomplete ischemic anoxia of the brain stem. Respiration continues because the posterior communicating arteries provide a collateral circulation. Additional occlusion of the carotid arteries causes medullary anoxia and respiratory arrest.

Repeated anoxia lowers the threshold of the respiratory neurones to its paralytic effects. Patterns of periodic breathing, resulting from ischemia or anoxemia of the brain under the conditions of these experiments, do not appear to be mediated by periodic fluctuations of oxygen availability of carotid body and respiratory center or rhythmic fluctuations in pH of the respiratory center. They appear to result from anoxic damage to various levels of the brain stem and are reversible.

Brief carbon monoxide breathing lowers the oxygen saturation of the blood without reducing the partial pressure of blood oxygen, the oxygen dissolved in the plasma may provide a critical supply sufficient for the metabolic needs of the respiratory center as the normal oxygen carrying capacity of the blood is slowly restored.

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REFERENCES

Breckenridge, C. G. and Hoff, H. E. Reflex respiration. *Amer. J. Physiol.*, **1954**, *178*: 521-528.

Clark, B. B., Van Loon, E. J. and Adams, W. C. Respiratory and circulatory responses to acute methemoglobinemia produced by aniline. *Amer. J. Physiol.*, **1943**, *139*: 64-69.

Comroe, J. H. and Schmidt, C. F. The part played by reflexes from the carotid body in the chemical regulation of respiration in the dog. *Amer. J. Physiol.*, **1938**, *121*: 75-97.

Comroe, J. H. The effects of direct chemical and electrical stimulation of the respiratory center in the cat. *Amer. J. Physiol.*, **1943**, *139*: 490-498.

Cooper, A. Some experiments and observations on tying the carotid and vertebral arteries and the pneumogastric, phrenic and sympathetic nerves. *Guy's Hosp. Rep.*, **1836**, *1*: 457-475.

Denny-Brown, D., Horenstein, S. and Fang, H. C. H. Cerebral infarction produced by venous distention. *J. Neuropath. Exp. Neurol.*, **1956**, *15*: 146-180.

Ganshirt, H., Sevenin, G. und Zylka, W. Der einfluss von sauerstaff, kohlensaure und glucose auf die schnappatmung der Ratte. *Arch. ges. physiol.*, **1952**, *225*: 283-293.

Gesell, R., Bicker, J. and Magee, C. Structural and functional organization of the central mechanism controlling breathing. *Amer. J. Physiol.*, **1936**, *117*: 423-452.

Haldane, J. S., Meakins, J. C. and Priestly, J. G. The effects of shallow breathing. *J. Physiol.*, **1919**, *52*: 433-453.

Haldane, J. S., Meakins, J. C. and Priestly, J. G. The respiratory response to anoxemia. *J. Physiol.*, **1919**, *52*: 420-432.

Haldane, J. B. S. Carbon monoxide as tissue poison. *Biochem. J.*, **1927**, *21*: 1068-1075.

Hill, L. *The Cerebral Circulation.* London, J. and A. Churchill, **1896.**

Heymans, C., Bouckaert, J. J. et Dautrebande, L. Sinus carotidien et réflexes respiratoires. II. Influences respiratoires réflexes de l'acidose, de l'alkalose, de l'anhydride carbonique, de l'ion hydrogène et de l'anoxemie. Sinus carotidiens et échanges respiratoires dans les poumons et au delà des poumons. *Arch. internat. Pharm. Thérap.*, **1930**, *39*: 400-448.

Heymans, C. Carotid sinus reflexes. Influence of central blood-pressure and blood supply on respiratory and vaso-motor centers. *J. Physiol.*, **1933**, *79*: 49-66.

Heymans, C. et Bouckaert, J. J. Survie et reviviscence des centres nerveux après suspension de la circulation. *Bull. Acad. roy. méd.*, Belgique, **1938**, *3*: 29-35.

Heymans, C. The role of the cardio-aortic and carotid sinus nerves in the reflex control of the respiratory center. *N. E. J. Med.*, **1938**, *219*: 157-159.

Hoff, H. E. and Breckenridge, C. G. The medullary origin of the respiratory periodicity in the dog. *Amer. J. Physiol.*, **1949**, *158*: 157-172.

Hoff, H. E. and Breckenridge, C. G. The neurogenesis of respiration, in Fulton, J. F., *Textbook of Physiology.* W. B. Saunders Co., Philadelphia, **1955**, 843-866.

Meyer, J. S., Fang, H. C. and Denny-Brown, D. Polarographic study of the cerebral collateral circulation. *Arch. Neurol. Psychiat.*, Chicago, **1954**, *72*: 296-312.

Meyer, J. S. and Denny-Brown, D. Studies of cerebral circulation in brain injury. I. Validity of combined local cerebral electropolarography, thermometry and steady potentials as an indication of local circulatory and functional changes. *EEG Clin. Neurophysiol.*, **1955**, *7*: 511-528.

Meyer, J. S. and Denny-Brown, D. Studies of cerebral circulation in brain injury. II. Cerebral concussion. *EEG Clin. Neurophysiol.*, **1955**, *7*: 529-544.

MEYER, J. S. Studies of cerebral circulation in brain injury. III. Cerebral contusion, laceration and brain stem injury. *EEG Clin. Neurophysiol.*, **1956**, *8*: 107-116.

MEYER, J. S., LEIDERMAN, H. and DENNY-BROWN, D. An electroencephalographic study of insufficiency of the basilar and carotid arteries in man. *Neurology*, **1956**. In press.

MEYER, J. S. and HUNTER, J. Effects of hypothermia on cerebral ischemia and hypoxia. *J. Neurosurg.*, **1957**. In press.

MEYER, J. S., WEGNER, W. and KANE, C. Clinical, electroencephalographic and arteriographic observations following surgical reconstruction of stenosis of the carotid artery in the neck. **1957**. To be published.

PAGANO, G. Sur la sensibilité du cœur et des vaissaux sanguins. *Arch. Ital. Biol.*, **1900**, *33*: 1-36.

PITTS, R. F., MAGOUN, H. W. and RANSON, S. W. The origin of respiratory rhythmicity. *Amer. J. Physiol.*, **1939**, *127*: 654-670.

PITTS, R. F. Organization of the respiratory center. *Physiol. Rev.*, **1946**, *26*: 609-630.

SCHMIDT, C. F. and COMROE, J. H. Functions of the carotid and aortic bodies. *Physiol. Rev.*, **1940**, *20*: 115-157.

SICILIANO, — Les effets de la compression des carotides sur la pression, sur le cœur et sur la respiration. *Arch. Ital. Biol.*, **1900**, *33*: 338-344.

SONNENSCHEIN, R. R., WALKER, R. M. and STEIN, S. N. A microglass electrode for continuous recording of brain pH in situ. *Rev. Sci. Instruments.*, **1953**, 702-704.

SWEET, W. H. and BENNET, H. S. Changes in internal carotid pressure during carotid and jugular occlusion and their clinical significance. *J. Neurosurg.*, **1948**, *5*: 178-195.

Reference: MEYER, J. S. Studies of cerebral circulation in brain injury. IV. Ischemia and hypoxemia of the brain stem and respiratory center. *EEG Clin. Neurophysiol.*, **1957**, *9*: 83-100.

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A MEASURABLE NEUROPHYSIOLOGICAL FACTOR OF PSYCHIATRIC SIGNIFICANCE [1]

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INTRODUCTION

The sedation threshold is a determination, which has both clinical and neurophysiological significance and which depends upon the EEG and speech changes produced by intravenously given amobarbital (Amytal) sodium (Shagass 1954). In a series of studies, it has been shown that the threshold is related to several psychiatric variables (Shagass 1954, 1956; Shagass and Naiman 1955, 1956). The two most important correlates may be formulated as manifest anxiety and impairment of ego functioning. The greater the degree of manifest anxiety, the higher the threshold; the greater the degree of impairment of functions involved in contact with reality (ego functions), the lower the threshold. In psychoneurotics the threshold also appears to be correlated with relative predominance of hysterical or obsessional traits in the personality, hysterics being at the low and obsessionals at the high end of the scale. These clinical correlations have made the sedation threshold of practical value as a test for psychiatric diagnosis. It has been most often applied to the problem of differentiating between neurotic and psychotic depressive reactions (Shagass, Naiman and Mihalik 1956).

Since the sedation threshold must reflect some factor which is of importance in the neurophysiology of psychiatric disorder, it would be desirable to define this factor as precisely as possible. The present study represents a step toward this goal. It was carried out to test the hypothesis that the sedation threshold is a function of the *rate of depressant action* [2] of amobarbital sodium on brain activity. According to this hypothesis, high thresholds would indicate a slow rate of depressant action and low thresholds a rapid rate. Although the hypothesis is implied in the concept of a "sedation threshold", it has not heretofore been subjected to test.

To confirm the hypothesis it would be necessary to show that an acceptable index of rate of depressant action is inversely correlated with the sedation threshold. Establishment of such an acceptable index presented a problem in itself. Most of the common indicators of depressant action of sedatives, which can be used in the intact human, are clinical signs, such as slurring of speech, nystagmus, or sleep. These are difficult to quantify; they are more easily judged as present or absent. The concept of rate implies a continuously varying function, and an ideal index of rate should permit one to measure the magnitude of a reaction at any point along a continuous gradient from zero to the fully developed reaction. Fortunately it was possible to show that the frontal fast frequency response to Amytal, which is measured to determine the sedation threshold, could, when averaged for groups of subjects, meet the requirements of an acceptable indicator of rate of depressant action. Data supporting this statement will be presented.

METHODS

Sedation Threshold Procedure. The test procedure has previously been described in detail (Shagass 1954). Amobarbital sodium is given intravenously at the rate of 0.5 mg/kg/40 sec. until well after slurred speech is noted. Continuous EEG's are recorded from transverse frontal and sagittal fronto-

[1] This investigation was supported by grants from the Department of National Health and Welfare and the Defence Research Board (Grant No. D.R.B. 9345-04, Project No. D50-93-45-04) of Canada.

[2] Rate of depressant action is an operational concept, stated in pharmacological terms. While it implies no specific neurophysiological mechanism, it can easily be interpreted within the framework of such neurophysiological concepts as excitability.

central placements. The amplitude of frontal fast activity is measured and plotted against the amount of drug. This usually yields a sigmoid curve (fig. 1, top), which contains a clear inflexion point, occurring about the time speech becomes slurred. The amount of Amytal, in mg/kg, required to reach this inflexion point is the sedation threshold. In earlier work all amplitude measurements were done on 10 per cent samples by means of an additive ruler. More recently measurements have been made on 50 per cent samples from the trace provided by an automatic integrator.[1]

Subjects. In order to permit valid comparisons of amplitudes, present data were restricted to tracings obtained from the same (bifrontal) leads. There were 299 such tracings among the first 440 technically valid initial tests on psychiatric patients, which were measured by the ruler method. There were also 45 tests on nonpatient control subjects. In addition, 100 consecutive tests on patients in which measurements were made by the integrator method, were analyzed. Diagnostic classification of subjects is shown in table I. The table includes only cases with ruler measurements, since a similar breakdown of the integrator cases would have resulted in groupings too small for statistical analysis. The diagnostic criteria were applied in a standard manner; they are described in detail elsewhere (Shagass 1956; Shagass and Naiman 1955, 1956; Shagass, Naiman and Mihalik 1956).

TABLE I

Means and Standard Deviations of Sedation Threshold and Amplitude of Frontal Fast Activity at Threshold Point in Relation to Diagnosis (Ruler Data)

Diagnosis	No. Cases	Sedation Threshold (mg/kg.) Mean	S.D.	Amplitude at Threshold (μV.) Mean	S.D.
Control Group	45	3.04	.682	16.0	5.04
Conversion Hysteria	19	2.89	.539	17.1	7.48
Hysterical Personality	10	2.90	.375	20.6	7.32
Hysterical Depression	8	2.63	.415	15.7	4.36
Mixed Neurosis	26	3.54	.636	17.4	5.48
Anxiety Hysteria	8	4.06	.728	17.5	6.92
Obsessive-Compulsive	9	4.22	.750	22.5	7.36
Neurotic Depression	30	4.98	1.013	19.0	7.18
Anxiety State	29	5.12	.807	18.6	6.93
Neurosis with Organic Features	7	2.79	.745	18.4	7.48
Alcoholism	8	4.25	1.000	19.7	10.27
Organic Psychosis	6	2.25	.250	17.6	8.48
Psychotic Depression (no ECT)	50	2.78	.703	19.8	7.68
Psychotic Depression (ECT)	7	3.07	.320	16.4	6.99
Schizo-affective	7	2.86	.515	21.2	7.72
Acute Schizophrenia	7	2.93	.418	14.7	3.46
Chronic Schizophrenia	31	4.19	1.040	19.5	6.58
Borderline Schizophrenia	26	4.92	1.260	18.8	7.48
Miscellaneous [1]	11	3.27		18.1	

[1] Includes: paraphrenia (3); manic state (4); psychopathic personality (3); morphine addiction (1).

RESULTS

The data were obtained by analyzing the interrelationships between the sedation threshold, psychiatric diagnosis, and amplitude of fast activity at different stages of the threshold determination.

[1] This integrator was designed by Dr. J. F. Davis. It employs two resonators of the type described by Ulett and Loeffel (1953). It integrates all frequencies between 17 and 25/sec. and writes out on a standard EEG channel. The integrating period is 0.5 sec., which permits rejection of samples contaminated by muscle artifact without excessive loss of data, as would occur with longer periods.

Relationship between the Sedation Threshold and Frontal Fast Activity Amplitude at Threshold. The amplitude of frontal fast activity induced by amobarbital varied widely from person to person; at the threshold point the range for ruler data was 4 to 50 μV. This wide variability of amplitude, which was noted early in the course of these studies, was the reason for using the shape of the amplitude curve, rather than absolute amplitude, as the criterion of sedation threshold. In present data the product-moment coefficients for correlations between the threshold and amplitude at the threshold point were .06 and .13 respectively for ruler and integrator data. Neither of these coefficients was statistically significant. This finding indicates that the sedation threshold was not a function of the absolute amplitude of fast activity at the threshold point. In fact, as signified by the lack of correlation between them, the mean amplitudes at threshold were about the same for all thresholds.

Relation to Psychiatric Diagnosis. Table I shows means and standard deviations of sedation thresholds and amplitudes of fast activity at threshold for the various diagnostic groups. The mean sedation thresholds varied considerably from group to group, while the mean amplitudes were relatively constant and were not systematically related to the threshold means. Excluding the "miscellaneous" one, there were 18 groups, allowing 153 comparisons of means. With respect to sedation threshold, 84 of the mean differences were significant at the 1 per cent level of confidence and 20 were significant at the 5 per cent level. The nature of these differences will not be detailed here, since they were in general agreement with those described in previous publications, referred to in the introductory paragraph of this paper.

In contrast to the numerous significant differences in sedation threshold, there were only seven statistically significant differences between the diagnostic groups with respect to mean amplitude at threshold. Four of these were at the 5 and three were at the 1 per cent level. The means of the control and acute schizophrenic groups were significantly lower than those of the obsessive-compulsive, psychotic depression, and chronic schizophrenic groups; the mean of the control group was also significantly lower than that of the neurotic depression group. It is doubtful whether these differences have any real significance, since five differences at the 5 per cent level would be anticipated by chance in 100 intergroup comparisons.

These data show that, while the sedation threshold differentiated between various psychiatric diagnostic categories with a high degree of reliability, the differences were not determined by fast frequency amplitude levels.

Influence of Initial Fast Frequency Amplitude. In the initial study of sedation threshold (Shagass 1954) it was noted that fast frequency amplitude at threshold was positively correlated with the amplitude before Amytal injection was started. Similar correlations for present data yielded coefficients of .68 for ruler and .77 for integrator material. This indicates that the greater the fast frequency amplitude in the pre-injection record, the greater the amplitude at threshold.

The correlation data for the integrator material were used to calculate the regression equation for predicting amplitude at threshold from pre-injection amplitude. Expected amplitudes at threshold, corresponding to given pre-injection amplitudes, were calculated from this equation. It was found that the actual amplitude at threshold was within 0.5 microvolts of the expected one in 57 per cent of the cases. Thus, in a fairly high proportion of cases, one could determine the sedation threshold by noting the amount of amobarbital required to produce a specified change from the pre-injection level of fast frequency amplitude. Pre-injection amplitude was itself not significantly correlated with the sedation threshold, so it could not be used to determine the threshold directly.

These data show that a great deal of the variability in amplitude of the fast frequency response to Amytal results from factors influencing amount of fast activity in the pre-injection record. If the effect of these factors were cancelled out, i.e., if pre-injection amplitude were held constant, the amplitude at threshold would be much less variable. However, the sedation threshold would not be altered if the variability in pre-injection amplitude were removed.

An Index for Rate of Depressant Action. For the individual subject the sedation threshold is determined from the inflexion point in the amplitude curve. Since this point is generally associated with slurred speech, the threshold point represents a particular level of depressant action of Amytal, which is defined in clinical and EEG terms. For groups of subjects, it would appear from the preceding data that a given mean amplitude of fast activity may also serve to indicate this particular level of depressant action. This follows from the fact that mean amplitude at threshold was relatively constant for subjects with different sedation thresholds. Since fast frequency amplitude usually increases continuously from the beginning of the injection to the threshold, the rate of this increase offered a potential index of rate of depressant action.

The first step in quantifying the rate index was to average the amplitude curves for all cases with a given threshold. This yielded a mean curve for every threshold, each with the typical sigmoid shape and a sharp inflection at the threshold. As examples, the curves for ruler data patients with thresholds of 2, 3, 4, and 5 mg/kg. are shown in the top half of figure 1. It will be noted that the mean amplitude at threshold is approximately the same for each curve and that the main difference between them consists in the rate at which the curve rises.

The second step was to replot the curves up to the threshold point in terms of the logarithm of amplitude. The bottom half of figure 1 shows the logarithmic points corresponding to the ones in the upper half of the figure. The straight lines drawn through the points were determined by the method of least squares (Guilford 1936). Plotted in terms of the logarithm of amplitude, the mean curves for each sedation threshold appeared to be rectilinear. As may be seen in the figure, the slopes of the straight lines differed. Now the slope of a rectilinear function represents the rate of increase of the dependent variable, in this instance fast activity amplitude. Consequently, the slope of the mean logarithmic amplitude curve could be taken as the required index of rate of depressant action of Amytal.

Test of the Rate of Depressant Action Hypothesis. Having established an index for rate of depressant action, all that remained to test the hypothesis was to determine the cor-

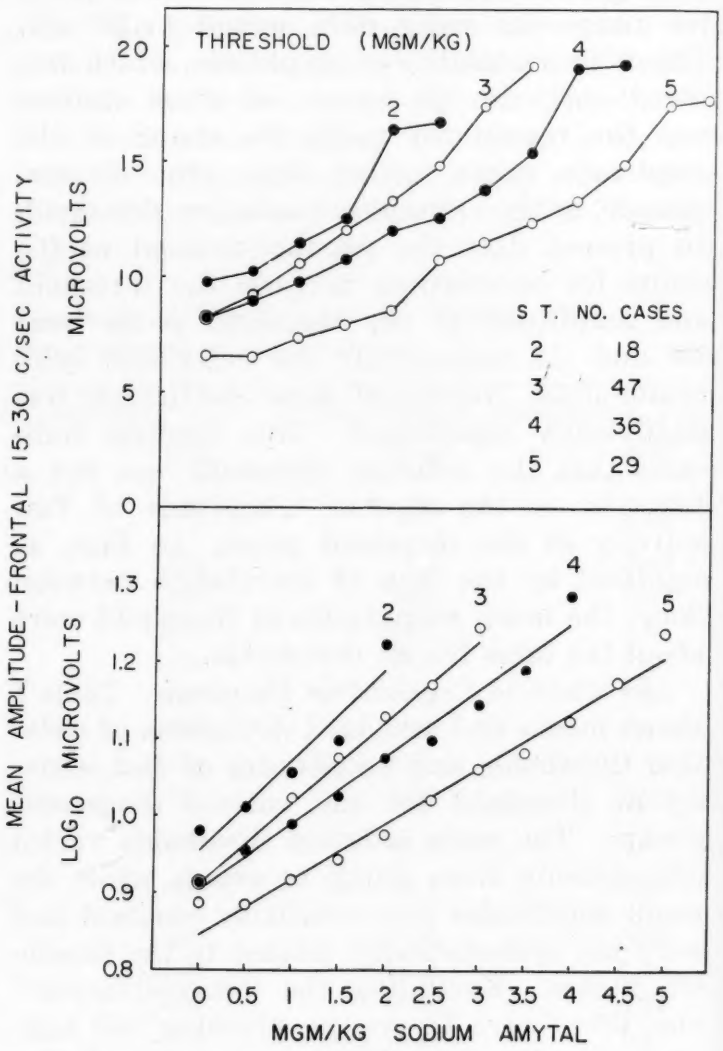

Fig. 1

Mean amplitude of fast activity as a function of amount of amobarbital. Upper curves, direct plot to one point beyond sedation threshold (S.T.). Lower curves plotted as log (amplitude) to S.T. Subjects include all patients with thresholds of 2, 3, 4 and 5 mg/kg. measured by ruler method.

relation between the sedation threshold and this index. Equations were calculated for the rectilinear function corresponding to each mean sedation threshold curve, as determined by the method of least squares. The general equation is $\log_{10} Y = a + b X$, where "Y" is amplitude in microvolts, "X" is mg/kg. of sodium amytal, "a" represents the initial or pre-injection amplitude of fast activity and "b" is the slope of the curve. The "b" constants, corresponding to each sedation threshold curve are shown in table II, together with numbers of cases upon which

curves were based. All data were from patients, and curves based on 3 cases or less were omitted. The data in table II are plotted in figure 2, together with the straight lines which best fit them. Rank-order correlation coefficients for the averaged data in table II

TABLE II

Slopes ("b" Constants) for Equations, log Y = a + bX, Corresponding to Each Sedation Threshold

Sedation Threshold (mg/kg)	Ruler Data		Integrator Data	
	No. Cases	"b"	No. Cases	"b"
1.5	5	.143	6	.187
2.0	18	.117	6	.172
2.5	41	.125	11	.148
3.0	47	.108	25	.143
3.5	47	.087	17	.105
4.0	36	.085	10	.110
4.5	31	.080	12	.097
5.0	29	.073	6	.102
5.5	21	.070	4	.075
6.0	5	.075		
6.5	5	.059		

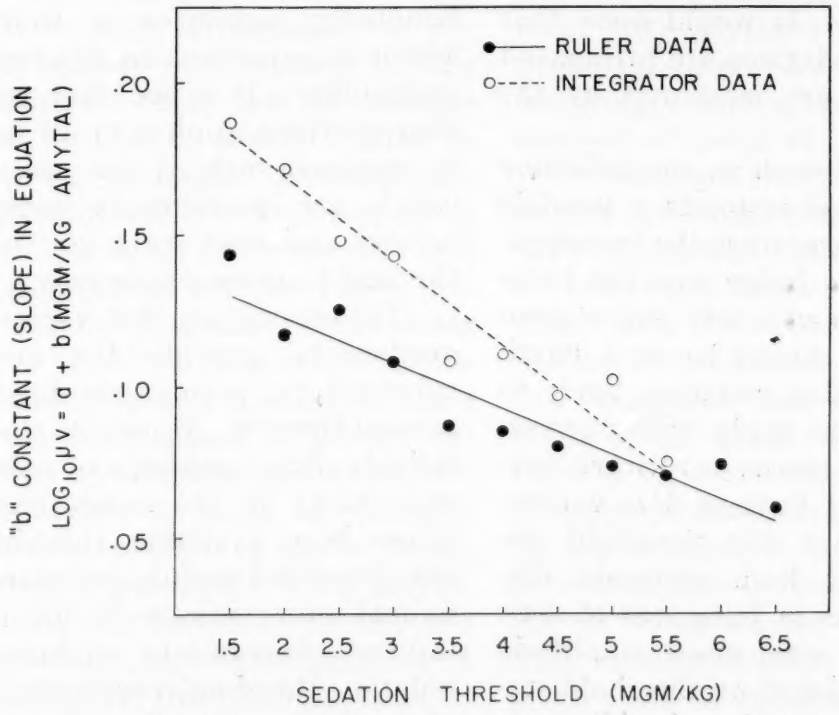

Fig. 2

Relationship between sedation threshold and slope of log (amplitude) function, which indicates rate of depressant action of amobarbital. Straight lines fitted by method of least squares.

were — .96 and — .97 for ruler and integrator respectively. These significant correlations and the approximation to rectilinearity of the relationships indicate that the sedation threshold was inversely proportional to the slope of the log (amplitude) function, which represented the rate of depressant action of amobarbital.

DISCUSSION

Present results demonstrated that the mean rate of increase in amplitude of the fast frequency activity produced by amobarbital could be taken as a valid index of rate of depressant action of this drug. By showing that this index was inversely correlated with the sedation threshold, the results confirmed the hypothesis that the sedation threshold measures rate of depressant action of amobarbital. This conclusion would probably also apply to thresholds determined with other barbiturates; in a small series of cases we found that secobarbital sodium yielded a threshold similar to the one with Amytal.

It should be noted that the fast wave index of depressant action probably applies only to the early stages of such action, i.e., before sleep. We have conducted no extensive studies in which injection of Amytal was systematically carried beyond the point of sleep. The impression gained from a number of incidental observations is that the changes in fast wave amplitude associated with onset of

sleep are not consistent. In many instances sleep coincides with a second rise in amplitude; such an effect was observed more frequently with rapid rates of injection (Shagass 1954). In a number of cases the amplitude curve shows no appreciable change with sleep, and sometimes amplitude decreases; the latter is probably due to a shift in frequency spectrum toward the low end.

Although this meaning of the term was not intended, one may question whether the sedation threshold can serve as an indicator of therapeutic sedative requirements. Available evidence on this point suggests that there is probably some overall correlation between the threshold and the sedative dose required for a given effect, such as inducing sleep. However, there appear to be many exceptions. For example, many subjects who fall asleep during the test do so shortly after their threshold is reached, but a number do not fall asleep when given two or three times the threshold dose. Also patients with agitated depression, who almost invariably have low thresholds, frequently find it hard to sleep even with high doses of sedatives. It would seem that the clinical effects of sedatives are influenced by more factors than are measured by the sedation threshold.

The use of slurred speech as one indicator of the sedation threshold suggests a possible criticism of the procedure, since the investigator might be inclined to judge slurring to be present in accordance with his expectation of what the threshold should be in a particular case. Also, the slur criterion tends to become more difficult to apply with increasing experience, as one learns to discern several grades of slurring. Present data contradict the possibility that the threshold determinations may have been seriously distorted by subjective bias in judgment of slur. It was shown that the same mean amplitude of fast activity was reached at threshold, regardless of the amount of amobarbital required. Consequently if one administered a fixed quantity of amobarbital to all subjects and measured fast frequency amplitude, without paying attention to slur, one could obtain the same differences between clinical groups as with the sedation threshold procedure which uses slur. It may also be noted that, in practice, especially since the integrator has been available, the possible error introduced by difficulty in judging slur has been reduced to a minimum by continuing the injection well beyond a definite slur point and relying upon the EEG curve for identification of the threshold.

It would be desirable to interpret the sedation threshold findings in terms of known neurophysiological mechanisms. In the absence of adequate information concerning the mechanisms of barbiturate action, this can be done in only a limited way. The two established properties which determine the depressant effects of barbiturates are: elevation of the threshold of neurones by stabilization of the cell membrane, and prolongation of the time for recovery from excitation (Goodman and Gilman 1955). Both properties are mechanisms for reducing neuronal excitability, but it is not known whether this is accomplished through augmentation of inhibitory processes, diminution of excitatory ones, or by a combination of both. In any case, the sedation threshold, which is inversely related to the rate at which excitability is reduced, undoubtedly measures a time characteristic which is important in determining degree of excitability. It is not clear whether this time characteristic applies to all neurones or only to systems, such as the ascending reticular, which are particularly sensitive to barbiturates and may serve as "pacemakers" for the fast frequency response.

The conception that variations in cerebral excitability provide the neurophysiological substrate for psychiatric disorders is basic to several theories. However, since almost no relatively direct methods of measuring cerebral excitability in the intact human have heretofore been available, thinking in this field has depended mainly on extrapolations from animal observations or on inferences from indirect observations on humans. While the sedation threshold represents only one index of cerebral excitability, it seems worthwhile to determine the extent to which the data provided by this single index agree with those obtained by other, more indirect, methods. Two approaches, which seem relevant, are those of Pavlov (1941) and Eysenck (1955).

In an address delivered in 1932, Pavlov made the following statement in connection with experimental neuroses:

"The best therapy against neuroses, in agreement with the findings of the clinic, are bromides, which according to our numerous and instructive experiments have a special relation to the inhibitory process, markedly reinforcing it. But the dose should be regulated accurately-for the strong type five to eight times greater than for the weak type" (1941, p. 92).

By "strong" or "weak" types Pavlov was referring to this classification of the nervous systems of dogs in terms of the form taken by experimental neuroses in these animals. He thus found that the weak or inhibitory type required considerably less sedative to be restored to normal behavior than the strong or excitatory type. Pavlov had earlier equated the weak type with hysteria and the strong type with neurasthenia. Since the sedation threshold is lower in hysteria than in all other neuroses, Pavlov's findings with bromides in dogs agree with present results with amobarbital in humans.

Following Pavlov's lead and utilizing a large body of objective psychological data, Eysenck (1955) recently formulated "a dynamic theory of anxiety and hysteria". This makes use of Hull's (1943) law of reactive inhibition, which in turn is closely related to Pavlov's concept of inhibition. Eysenck postulated that individuals differ with respect to the speed of production, the strength, and the speed of dissipation of reactive inhibition. He further postulated that those individuals in whom reactive inhibition is generated more quickly, more strongly, and dissipated more slowly are thereby predisposed to develop extraverted patterns of behavior and hysterico-psychopathic disorders in cases of neurotic breakdown; conversely, individuals in whom reactive inhibition is generated more slowly, more weakly, and dissipated more rapidly are predisposed to develop introverted patterns of behavior and dysthymic disorders in cases of neurotic breakdown. "Dysthymic" disorders include the obsessive-compulsive neuroses, anxiety states and neurotic depressions. Eysenck demonstrated differences between hysterics and dysthymics in conditioned responses and perceptual after-effects which were in accord with predictions from his theory. He also postulated that brain damage would increase reactive inhibition and showed that brain injured subjects were indeed similar to hysterics and extraverts on relevant tests.

The close similarity between Eysenck's introversion-extraversion findings in psychoneurotic patients and the results with the sedation threshold in such patients has been discussed elsewhere (Shagass and Naiman 1956). These two widely different methods of measurement arranged the different types of neurosis in almost identical order, so that it seems highly probable that the sedation threshold measures a factor closely allied to introversion-extraversion. In addition to the order, the *direction* of the differences between groups was in accord with Eysenck's theory, if it is granted that amobarbital is an inhibitory agent in the sense of behavioral inhibition. From the theory one would predict that hysterics, with a high degree of reactive inhibition, would require less amobarbital to reach a given depressant threshold than dysthymics. This prediction agrees with the facts. The very low sedation thresholds found in cases of organic psychosis are also in agreement with Eysenck's theory. Furthermore, present data on *rate* of depressant action are temptingly analogous to the behavior-based concept of *speed* of reactive inhibition.

It will be noted that the considerable apparent agreement between the sedation threshold findings and those of Pavlov and Eysenck depends upon linking the depressant action of drugs with their concept of inhibition. There can be little objection to doing so, providing one recognizes that the link is essentially in terms of the similarity of behavioral observations in their investigations and in the clinical phenomena associated with depressant drugs. At the neurophysiological level, it has seemed more desirable to consider the sedation threshold in terms of the concept of excitability. This concept allows the assumption that a given state of excitability results from interaction of excitatory and inhibitory processes. However, it has the advantage of not requiring specification of the extent to which each of these processes may be participating at any one time, something which cannot be done at present. It will be the task of future research to specify the parameters of excitability which are most pertinent to psychiatric disorder. The concordance between results obtained by

such different methods as those of Pavlov, Eysenck and the present one indicates that they study similar basic phenomena, which should be amenable to a clinical neurophysiological approach.

SUMMARY

1. The sedation threshold is a clinical neurophysiological test, which determines the amount of intravenous amobarbital sodium required to produce certain EEG changes, accompanied by slurred speech. Previous investigations have shown the threshold to be related to several significant psychiatric variables, such as degree of manifest anxiety. The purpose of the present study was to further the aim of defining the neurophysiological factor, measured by the sedation threshold, by testing the hypothesis that the threshold is a function of the rate of depressant action of amobarbital on brain activity.

2. An acceptable index of rate of depressant action was required to test the hypothesis. Analysis of data from 399 psychiatric patients and 45 nonpatient subjects showed that the amplitude of frontal fast frequency activity, produced by amobarbital, could provide such an index. The mean amplitude at the threshold, which represents a particular level of depressant action, was approximately constant for groups of subjects with different thresholds. The rate of increase of mean amplitude, which could be taken as the index of depressant action, was amenable to quantitative expression as the slope of a rectilinear function, when the logarithm of amplitude was used in calculation. In confirmation of the hypothesis, there was a highly significant inverse correlation between the sedation threshold and this index of rate of depressant action.

3. In contrast to the sedation threshold, fast frequency amplitude as an absolute value, either before the injection or at threshold, was not significantly related to psychiatric diagnosis. Amplitude at threshold was correlated with amplitude before injection, but neither value was significantly correlated with the sedation threshold.

4. From the conclusion that the sedation threshold is a function of rate of depressant action of amobarbital, it was suggested that it measures a time characteristic of neuronal activity, which is probably an important factor influencing cerebral excitability. The extent to which the sedation threshold findings agree with neurophysiological theories of psychiatric disorder derived from behavioral observation was considered.

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REFERENCES

EYSENCK, H. J. A dynamic theory of anxiety and hysteria. *J. Ment. Sci.*, **1955**, *101*: 28-51.

GOODMAN, L. S. and GILMAN, A. *The Pharmacological Basis of Therapeutics,* New York, MacMillan, **1955**.

GUILFORD, J. P. *Psychometric Methods.* New York, McGraw-Hill, **1936**.

HULL, C. L. *Principles of Behavior.* New York, D. Appleton-Century, **1943**.

PAVLOV, I. P. *Conditioned Reflexes and Psychiatry,* Transl. by W. H. Gantt, New York, International Publishers, **1941**.

SHAGASS, C. The sedation threshold. A method for estimating tension in psychiatric patients. *EEG Clin. Neurophysiol.*, **1954**, *6*: 221-233.

SHAGASS, C. The sedation threshold. A neurophysiological tool for psychosomatic research. *Psychosom. Med.*, **1956** (in press).

SHAGASS, C. and NAIMAN, J. The sedation threshold, manifest anxiety, and some aspects of ego function. *Arch. Neurol. Psychiat.*, Chicago, **1955**, *74*: 397-406.

SHAGASS, C. and NAIMAN, J. The sedation threshold as an objective index of manifest anxiety in psychoneurosis. *J. Psychosom. Research,* **1956**, *1*: 49-57.

SHAGASS, C., NAIMAN, J. and MIHALIK, J. An objective test which differentiates between neurotic and psychotic depression. *Arch. Neurol. Psychiat.*, Chicago, **1956**, *75*: 461-471.

ULETT, G. A. and LOEFFEL, R. G. A new resonator-integrator unit for the automatic brain wave analyzer. *EEG Clin. Neurophysiol.*, **1953**, *5*: 113-115.

Reference: SHAGASS, C. A measurable neurophysiological factor of psychiatric significance. *EEG Clin. Neurophysiol.*, **1957**, *9*: 101-108.

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ELECTROENCEPHALOGRAM IN NARCOLEPSY [1]

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Narcolepsy is a disease characterized by episodes of sleep usually of brief duration but recurring many times daily. In many instances there are associated cataplectic attacks characterized by loss of muscle tone without change in consciousness. These attacks are commonly induced by laughter, anger, fright or startling stimuli. Episodes of so-called sleep paralysis may occur while falling asleep or awakening; during these the patient is conscious but unable to move. Many patients with narcolepsy are also subject to hypnagogic hallucinations and nightmares.

Although narcolepsy is a relatively common disease, it has received surprisingly little attention from electroencephalographers. Blake, Gerard and Kleitman (1939) studied 11 cases and noted that, when the patients were examined while in a sitting position, the electroencephalogram was within normal limits. However, when the patients were allowed to lie down, drowsiness occurred within a short time. Later Dynes and Finley (1941) examined 22 patients. Of these, 17 had classic idiopathic narcolepsy. Sixteen of these 17 patients had narcoleptic attacks during the electroencephalographic recording. The authors commented that the electroencephalographic patterns observed during these attacks were in all instances similar to those seen during physiologic sleep. The authors concluded that there were no significant abnormalities in the electroencephalograms of patients with idiopathic narcolepsy.

On the other hand, Cohn and Cruvant (1944), from the study of 10 patients, concluded that the electroencephalograms showed "inconstant but definite abnormalities". In their opinion, the records of these patients resembled those of patients with epilepsy. However, they regarded the sleep of the narcoleptic patient as fundamentally normal and a manifestation of physiologic sleep. Careful examination of their findings suggests that in some instances their patients were drowsy although not actually asleep and that they may have misinterpreted as abnormal certain stages of physiologic drowsiness. Stoupel (1950) reported on seven patients, in the majority of whom the electroencephalograms were abnormal and similar to those of epileptic patients.

Pond (1952), in a more recent study based on eight patients on whom a large number of electroencephalograms were recorded, felt that the records were normal but exhibited frequent "drifts" into a phase typical of early sleep. During actual sleep itself he observed the records to be normal. He, therefore, concluded with the earlier authors that the electroencephalograms of narcoleptics are essentially normal and that there is no evidence that narcolepsy is related to epilepsy.

Other investigators have dealt incidentally with the electroencephalogram in narcolepsy. Murphy (1941) stated that the electroencephalogram shows little evidence of pathologic cerebral dysrhythmia. Roth (1946) presented an interesting case with a spike-and-wave type of discharge in a narcoleptic patient with a history of short periods of sudden loss of consciousness. Aird, Gordon and Gregg (1953) reported on the use of phenacemide in the treatment of 6 patients with narcolepsy and cataplexy and commented that the electroencephalogram was essentially within the limits of normal when the patient was awake but showed a slight, generalized cerebral dysrhythmia of the type usually associated with drowsiness when the patient was clinically drowsy.

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[1] Read at the meeting of the American Electroencephalographic Society, Atlantic City, New Jersey, June 15 to 17, 1956.

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In view of these contradictory opinions, both as to the character of the waking electroencephalogram in narcoleptic patients and as to the relationship of narcolepsy to epilepsy, further study of this problem seems to be justified.

MATERIAL AND TECHNIQUES

The electroencephalograms of 100 patients with the clinical diagnosis of narcolepsy were examined for this study. We shall not review the clinical characteristics of this group in detail, since they are included in a larger series of 241 patients on whom we shall publish elsewhere a clinical report. Suffice it to say that in all patients the diagnosis of narcolepsy was established clinically and that this subgroup of patients studied electroencephalographically did not differ in any essentials from the entire group of 241 patients. This series was compiled by selecting consecutively the records of 100 patients from the files of the electroencephalographic laboratory during the years 1950 to 1954. Sixty-four of the patients were male and 36 were female. The table illustrates the distribution by age at the time that the electroencephalogram was made. The decade of age in which there was the largest number of patients was 31 to 40 years. Clinically, narcolepsy alone occurred in only 15 per cent of patients. In the remaining 85 per cent of the patients the narcolepsy was associated with other symptoms of cataplexy, sleep paralysis or nightmares in varying combinations. The most frequent combination, occurring in 37 per cent of patients, was narcoleptic and cataplectic attacks. The full tetrad of symptoms occurred in 16 per cent of patients.

TABLE

AGE DISTRIBUTION OF 100 PATIENTS WHO HAD NARCOLEPSY

Age, years	*Patients*
10 or less	1
11 to 20	14
21 to 30	25
31 to 40	31
41 to 50	15
51 to 60	6
61 to 70	8

Recordings were made on 8-channel model IV Grass electroencephalographs. A total of 14 electrodes was employed. These were arranged in the following fashion: 5 pairs of parasagittally placed electrodes equally spaced from frontal to occipital regions, one pair of electrodes in the sylvian regions and one pair of electrodes on the ears. Varying combinations of scalp-to-scalp and scalp-to-ear linkages were employed. The examination was conducted routinely with the patients in a sitting position and the technician and electroencephalograph in the same room with the patients. The patients were asked to keep their eyes closed, but for a period of 10 sec. on each of the runs they were asked to open their eyes. At the end of the recording with the various routine combinations of electrodes, the patients were asked to perform simple mental calculations in order to enable us to determine the effect of mental activity. Following this, the patients performed hyperventilation in the routine manner. Two minutes after the cessation of hyperventilation, photic stimulation was carried out. A photic stimulator producing a brief, intense flash of light was employed. Stimulation was carried out for 10 sec. at each of 10 different frequencies varying between 1 and 30 c/sec. This was performed first with the patient's eyes open and subsequently with the eyes closed. No attempt was made to permit the patients to go to sleep during the routine recording, and the method of obtaining the recording was that normally employed in the laboratory for routine examination.

RESULTS

Under circumstances which will ordinarily permit a normal person or patient without narcolepsy to go to sleep, the phase of drowsiness is a relatively brief one through which the patient passes on the way to light sleep. Davis and his colleagues (1938), in studying normal persons, reported that the earliest manifestation of drowsiness is spindling of the alpha rhythm. Following this, there is flattening of the record with disappearance of the alpha rhythm. The record, at this

stage, shows slow-wave discharges, usually within the theta range. Following this phase, the patient passes into the stage of so-called "V waves" and finally, into the stage in which spindles are seen. There are some variations, depending on age, in the pattern of drowsiness and light sleep. These have been summarized by Gibbs and Gibbs (1950). Allowance was made for this in the interpretation of the recordings; however, since 77 per cent of our patients were between the ages of 21 and 60 years we shall devote our major consideration to this adult group. The characteristics of these various stages of descent into sleep are illustrated in figure 1, in which one of our narcoleptic patients was permitted to fall asleep.

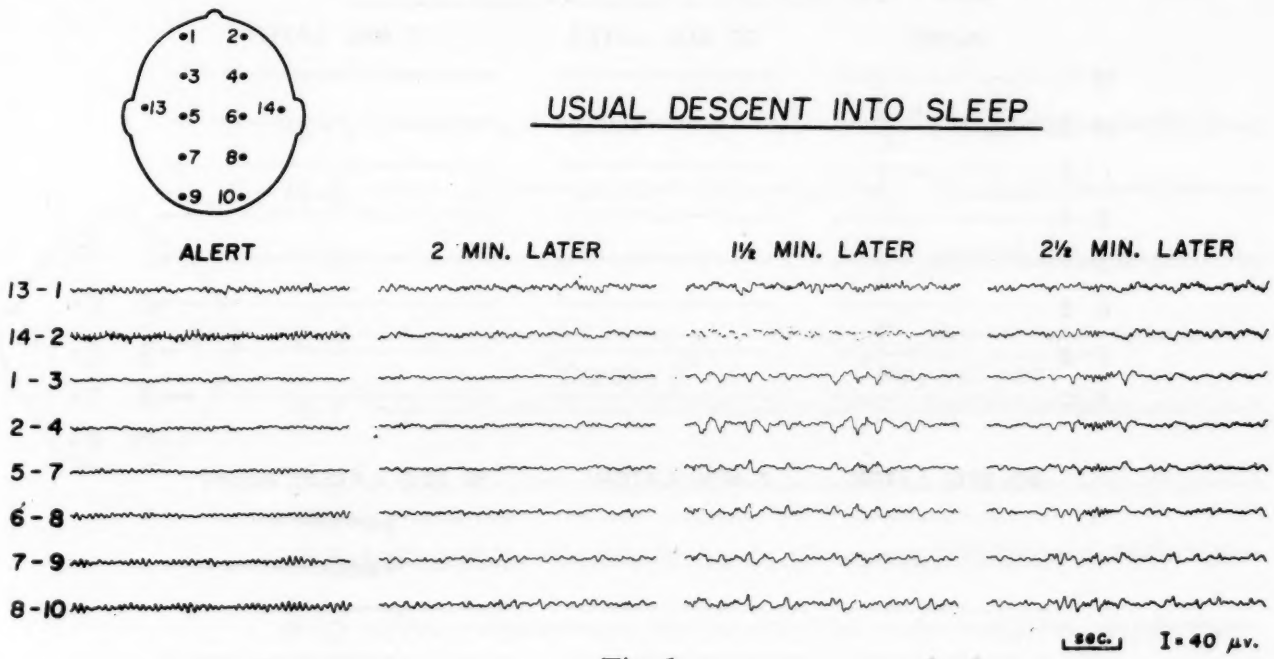

Fig. 1

This 27-year-old male schoolteacher had noted the onset of recurrent episodes of sleepiness 9 years previously while serving in the Army. At age 24 years attacks of mild generalized weakness had developed; these were precipitated by anger, laughing and violent physical exertion.

However, under the recording conditions which we have previously described for this study, sleep was uncommon and occurred in only five patients. On the other hand, drowsiness was extremely frequent; 83 per cent of all patients manifested electroencephalographic evidence of drowsiness at some time during the recording. These figures become even more striking when the circumstances of the drowsiness are noted. Twenty per cent of the patients appeared drowsy at the moment that the recording was begun, in spite of the fact that they had just been seated in the chair, their electrodes connected with the plug box and instructions given to them for the test. In non-narcoleptic patients, drowsiness at this time rarely occurs. In the first 4 min. of the recording an additional 41 patients had become drowsy and within 12 min. 75 per cent of patients had been drowsy. The pattern of drowsiness, once established, tends to recur throughout the remainder of the recording period. The record then tends to alternate between the alert state with a well-defined alpha rhythm and the drowsy state. Extraneous noises in the laboratory, the commands to open and close the eyes and the urgings of the technician for the patient to stay awake usually produce only a transient activation of the record. In many instances drowsiness recurs within seconds after the patient has been alerted. On the other hand, even if left undisturbed the majority of narcoleptics will not fall asleep in the laboratory environment. Instead they will remain in the drowsy phase for protracted periods up to 30 min. or more. During this time they

may rouse for brief periods, only to drift off once again. We regard the phenomenon of persistent drowsiness (fig. 2) with the patient suspended as it were in limbo, neither asleep nor alert, as characteristic of narcolepsy.

As we have mentioned, frank sleep on the contrary was rare and occurred in only 5 patients. These patients fell asleep one or more times during their recording under the following circumstances: 4 patients fell asleep while counting aloud in an effort to stay awake; 3 patients fell asleep while carrying out hyperventilation; and one patient fell asleep during photic stimulation.

In 7 patients the opportunity presented itself to make more than one recording. At the time of the second recording 6 of the 7 patients again exhibited episodes of drowsiness.

In spite of the frequent occurrence of drowsiness, the patients themselves often seemed unaware of this. This was frequently apparent during examination of the patients in the laboratory. On many occasions the technician would note that the patient was

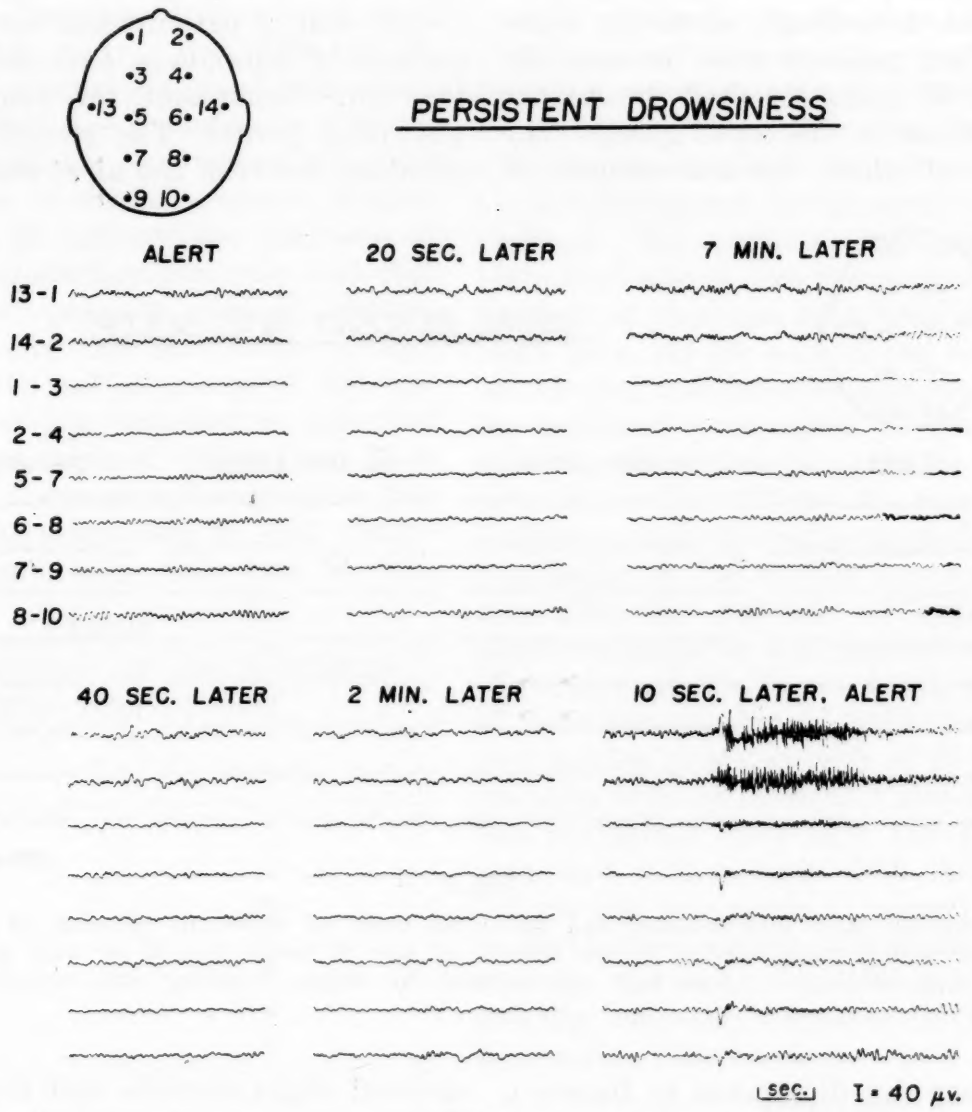

Fig. 2

The history of this patient is given in figure 1. Note that throughout the 10-min. period represented in the recording the patient showed fluctuating drowsiness; yet, at the end of that time stimulation of the patient produced an alerting with return of the record to the basal state.

nodding or appeared drowsy; yet on direct questioning the patient would deny that this was the case and would seemingly be unaware of his behavior. In other instances there was electroencephalographic evidence of drowsiness which disappeared when the patient was asked if he were drowsy. The recording was then typical of the alert state. Again, in these instances, the patient was frequently unaware that he had been drowsy. This is illustrated in figure 3. Further confirmation of this unreliability on the part of the patient it were, acclimated and hence unaware of their drowsiness.

While normal persons may become drowsy during the electroencephalographic examination, relatively simple procedures, such as speaking to the patients or having them open their eyes, suffice, in most instances, to restore them to the alert state. On the other hand, in narcoleptic patients such procedures are almost invariably ineffective. As we have already mentioned, speaking to the patient frequently restores the record to the alert

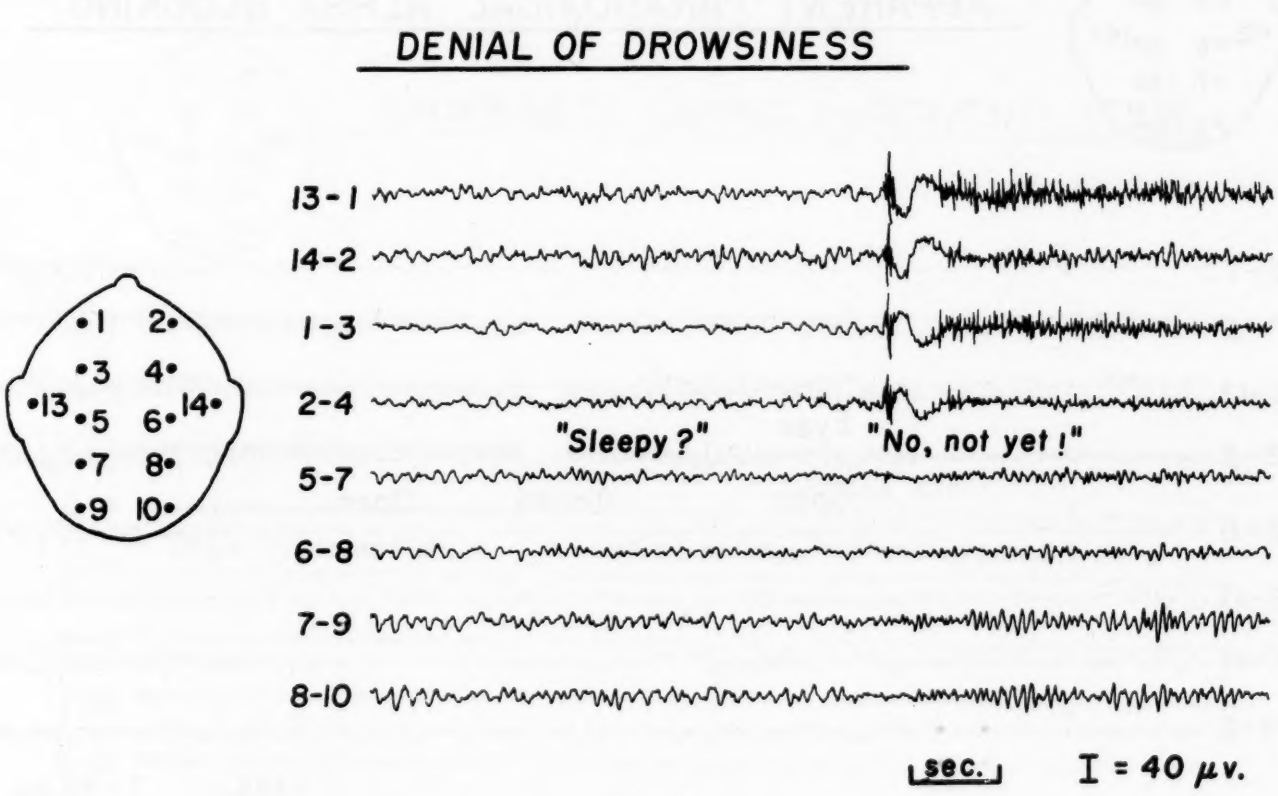

Fig. 3

This 61-year-old housewife had had frequent narcoleptic attacks for the preceding 20 years. When surprised, she would experience generalized weakness.

is found in the patient's own estimate of the severity of his narcolepsy as compared with electroencephalographic evidence of drowsiness during the examination. Of the patients who regarded their narcolepsy as severe, 93 per cent showed evidence of drowsiness at some time during the examination, but surprisingly, of the patients who classed their narcolepsy as mild, 70 per cent showed evidence of drowsiness during the examination. This suggests that chronic drowsiness in these patients is so common that they become, as state but drowsiness returns within seconds or at most a minute or two. In many of the narcoleptic patients the command to open the eyes is sufficient to arouse the patient and produce a return of the alpha rhythm in the record. The patient may then remain alert for a few more seconds or a half minute before becoming drowsy. However, in a few patients the effect of eye opening and the associated alerting was extremely brief and drowsiness recurred almost immediately after eye closing. This gave to the record an ap-

pearance of what might be called "paradoxical" blocking of the alpha rhythm. Such a situation is illustrated in figure 4. In this patient the command to open the eyes was associated with alerting and the reappearance of the normal alpha rhythm. Almost immediately after eye closing, the patient again became drowsy and the alpha rhythm disappeared. Therefore, in this patient, the alpha rhythm appeared to be induced by eye opening and inhibited on closing the eyes.

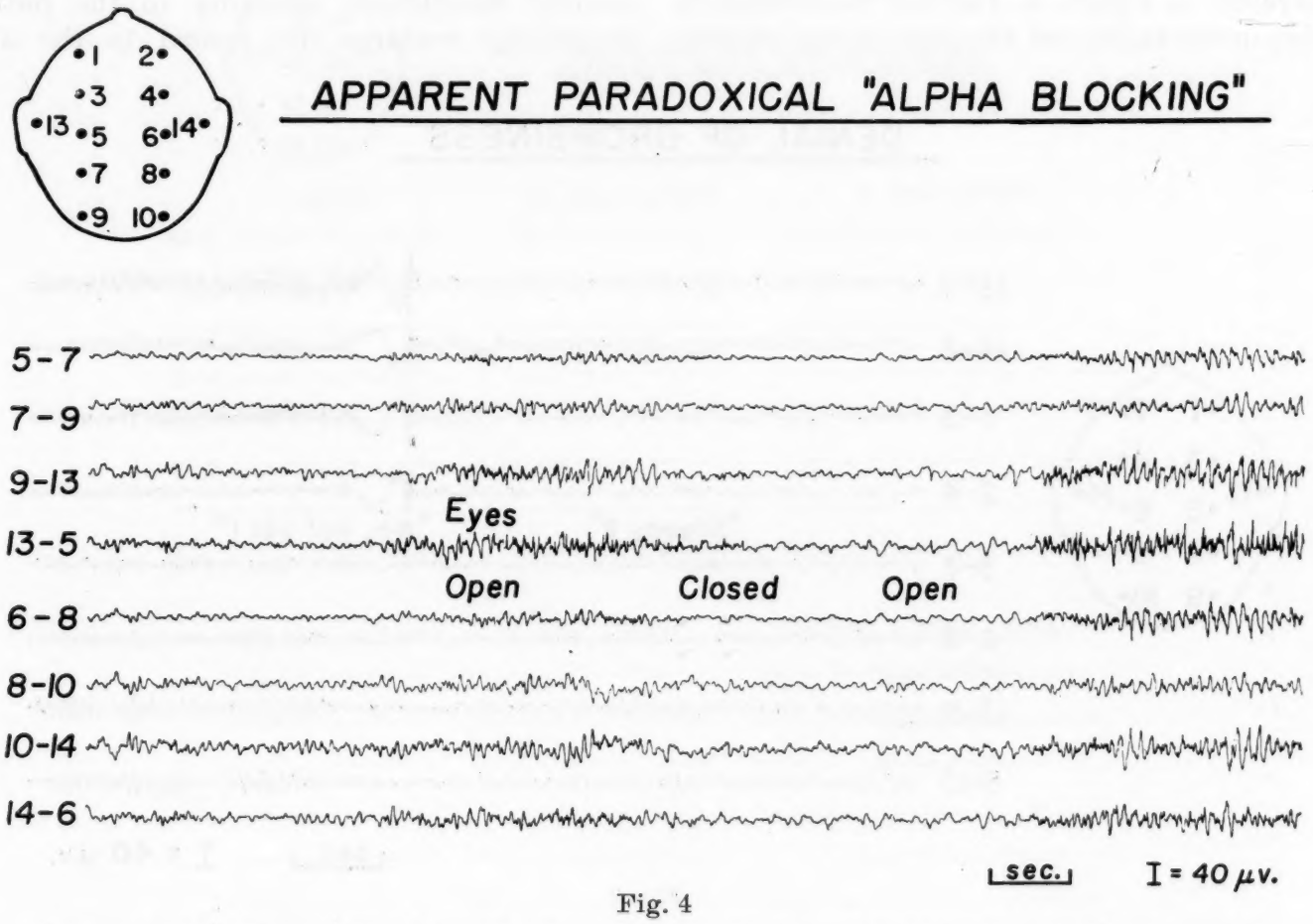

Fig. 4

The patient, a 39-year-old housewife, first had narcoleptic and cataplectic attacks at age 30 years. Four years after the onset she had first experienced sleep paralysis and vivid nightmares.

One might expect that such vigourous physical activity as hyperventilation would be sufficient to arouse the patient and keep him alert throughout the interval during which he is performing it. However, such was not the case, and in 26 per cent of patients drowsiness was observed during the act of hyperventilation (fig. 5). In many of these patients there was no obvious slowing or alteration of the respiratory rate in spite of drowsiness. Yet, if these patients were spoken to, the record would become altered toward the alert state. Several of the patients were also noted to be nodding during hyperventilation, although they did not actually cease overbreathing. In other patients, however, there was slowing or actual cessation of hyperventilation. As was previously mentioned, three patients fell asleep during hyperventilation (fig. 6). In the period following the cessation of overbreathing, when there were fewer stimuli to alert the patient, drowsiness became more frequent and almost one half (42 per cent) of the patients became drowsy at this time.

One might logically expect that an external stimulus, such as a bright flashing light, would be sufficient to maintain alertness. Here again, however, drowsiness was com-

mon and occurred in 19 of 89 patients on whom photic stimulation was carried out while their eyes were open. In this same group photic stimulation, done when the eyes were closed, led to drowsiness in 51 patients (fig. 7).

Attempts to keep the patient alert by having him count aloud were also ineffective in many instances. A number of patients would exhibit slowing and finally cessation of the counting and, as was previously noted, 4 patients fell asleep while counting aloud.

desired to record in the so-called basal or alert state the most effective maneuver is to permit the narcoleptic patient to drowse off for a short period. In many of these patients, permitting them to drowse undisturbed for 5 or 10 min. is sufficient to relieve the impulse to sleep. Following this, the patient will remain alert and satisfactory recording in the basal state may be obtained.

When recordings can be obtained with the patient thoroughly alert and free of drowsiness, the records of the narcoleptics as a

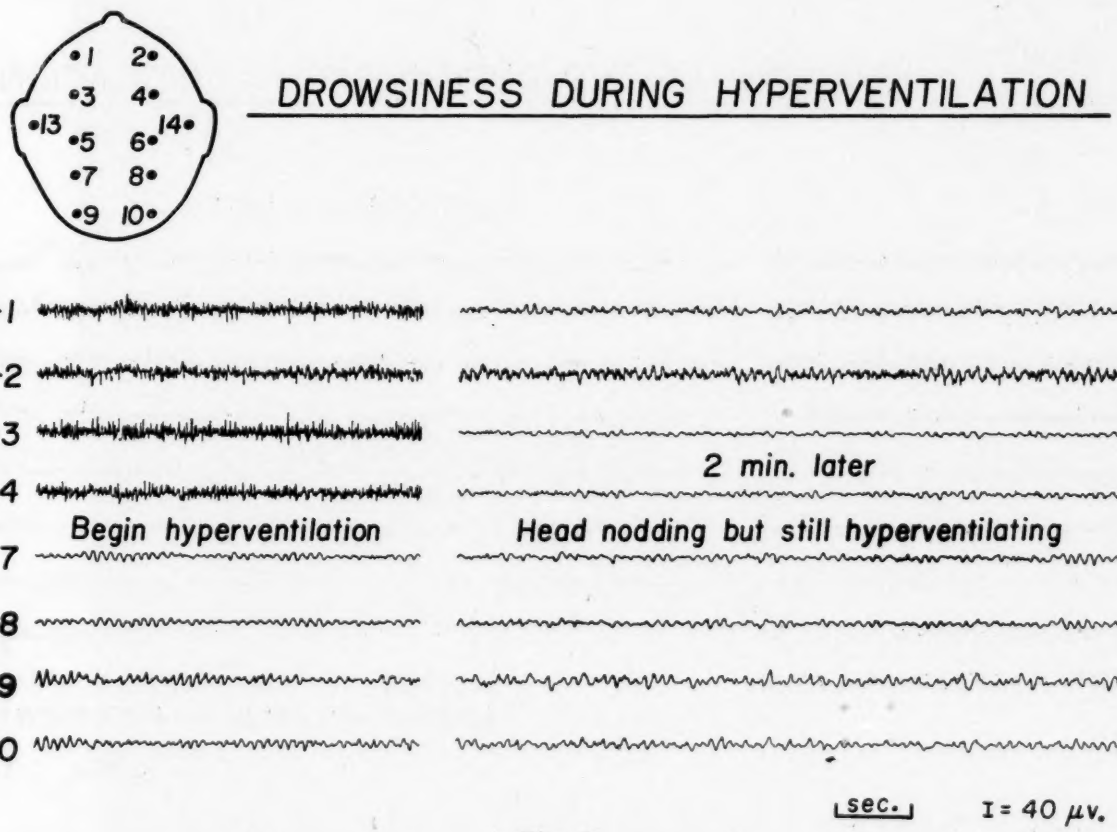

Fig. 5

Since adolescence this 38-year-old housewife had been subject to episodes of irresistible sleep occurring several times daily. She was also subject to cataplexy.

The impulse to drowsiness is almost irresistible in the narcoleptic patient and cannot be prevented even by the various procedures that we have described. Under ordinary circumstances these are sufficient to keep the non-narcoleptic subject alert throughout the examination, but once the narcoleptic patient has become drowsy it is almost impossible to maintain his alertness and obtain a satisfactory recording of the electroencephalogram in the alert state. We have found that if it is

group are unremarkable and indistinguishable from those of a normal control group. In the alert state the alpha rhythm usually was of normal frequency. In 96 of the patients the alpha rhythm was between 8 and 11 c/sec., the peak incidence (77 per cent) being between 9 and 10 c/sec. In only one adult patient was the dominant occipital rhythm less than 8 c/sec. In 3 patients the record was of the low-voltage type without discernible alpha rhythm. In 86 of the patients the

records were felt to be typically normal while in 12 patients low to medium voltage 5 to 7 c/sec. rhythms appeared at times when the patient was believed to be alert. In only 2 patients was the record felt to be grossly abnormal with the dominant rhythms in the 4 to 7 c/sec. range. Thus, we believe that in the alert state the electroencephalograms of this group of patients are not abnormal. In no instance was there evidence of focal abnormality, and in no patient was there any evidence of spike-and-wave or spike discharges.

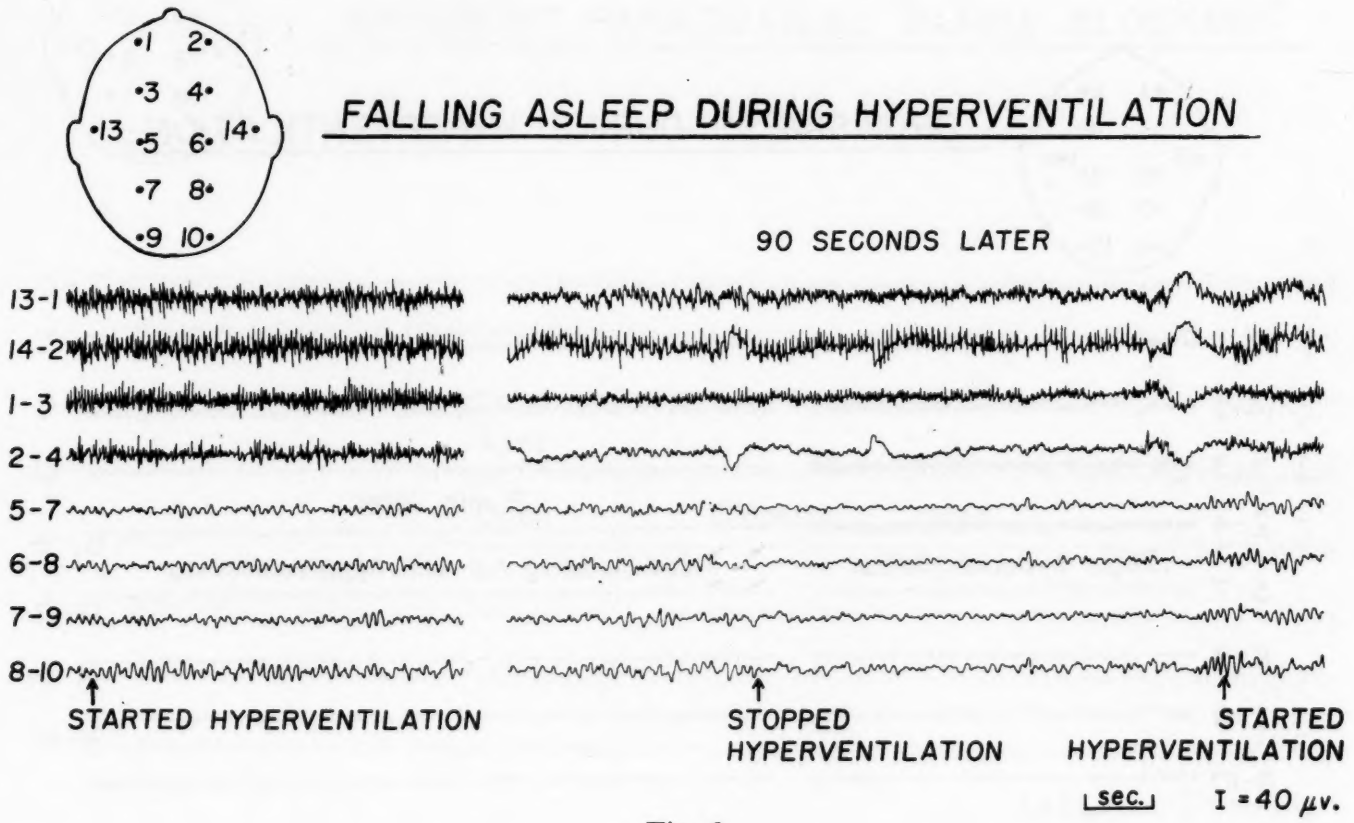

Fig. 6

The history of this patient is summarized in figure 5. This recording was made at the time of a second examination of this patient. At the time of the original examination she had shown drowsiness during hyperventilation.

There exist, however, pitfalls for the unwary which may lead to erroneous interpretations of the electroencephalogram. These consist primarily of failure to recognize the tendency to sustained drowsiness that characterizes these patients. The fact that drowsiness may be present from the moment the recording is begun and may persist throughout the recording without effective alerting of the patient may lead to the misapprehension that the record shows generalized slowing. This confusion may be compounded by the failure of eye opening and hyperventilation to produce any sustained alerting of the patient. On other occasions the technicians have been led astray when the patient was referred with a diagnosis of possible epilepsy. In some instances, the technicians have mistaken episodes of drowsiness with head nodding for akinetic seizures. The movement artifact in the electroencephalogram which was produced by the sudden dropping of the head has been erroneously interpreted as cortical potentials. Examination of these patients therefore demands alerting, not only of the patient, but of the technician and the electroencephalographer as well.

In the present study we have attempted to examine these patients in the basal or alert state and prevent their going to sleep. In a few instances we were able on a subsequent

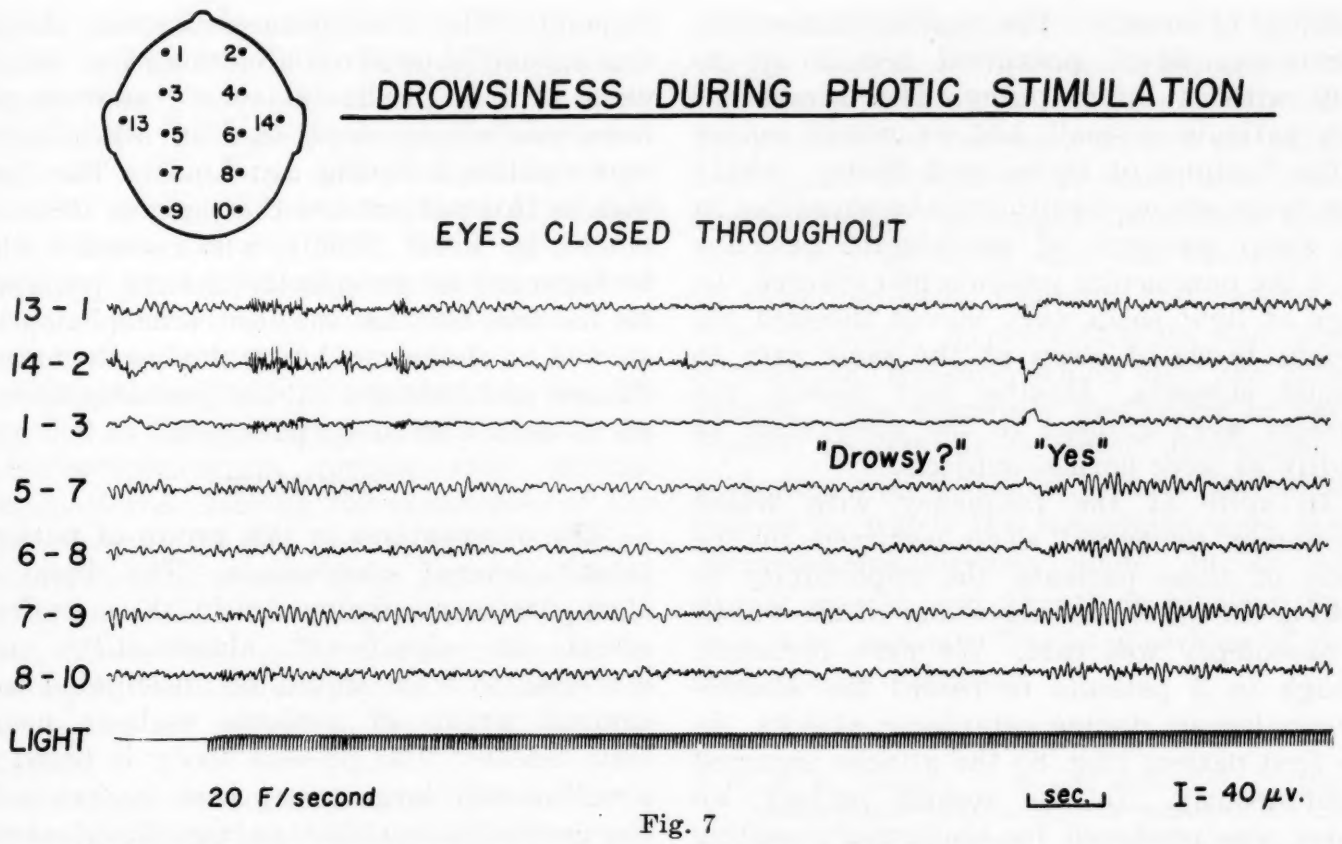

Fig. 7

A 30-year-old male insurance agent had experienced 2 to 6 attacks of sleep per day for the preceding 4 years. One year after the onset of the narcolepsy the patient had noted weakness of the lower extremities whenever he laughed or became angry; on several occasions the weakness was severe enough that he fell.

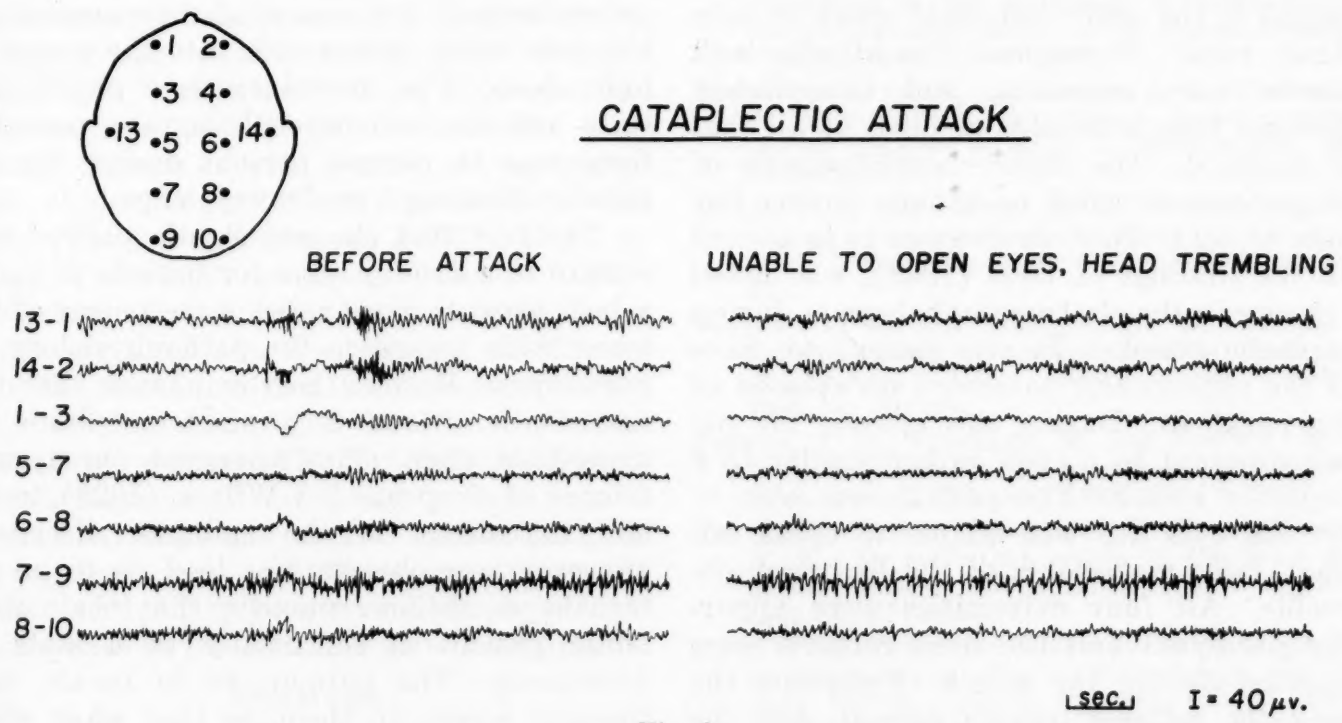

Fig. 8

Two years previously this 61-year-old woman had noted narcoleptic attacks occurring 2 to 3 times daily and occasional episodes of generalized weakness precipitated by laughter, anger or any startling stimulus. She was also subject to episodes of sleep paralysis.

occasion to examine the patient under circumstances which permitted him to go to sleep without interruption. The number of such patients is small, but we would concur in the findings of Dynes and Finley (1941) that there are no significant abnormalities in the sleep patterns of narcoleptic patients. Once the narcoleptic patients had entered the stage of light sleep, they moved through the various levels of sleep at the same rate as normal subjects. Having been asleep, the patients were aroused to the alert state as readily as were normal subjects.

In spite of the frequency with which drowsiness or actual sleep occurred in the study of these patients, the opportunity to observe the other manifestations of the tetrad of narcolepsy was rare. We were fortunate enough in 2 patients to record the electroencephalogram during cataplectic attacks. In the first patient (fig. 8) the attacks occurred spontaneously. In the second patient, an attack was produced by accidentally calling the patient by the wrong name; she found this annoying. Repetition of this would each time induce a typical cataplectic attack characterized by dropping of the head and a general relaxation of the body musculature so that she slumped in the chair and could speak in only a faint voice. Throughout the attacks both patients were conscious, and immediately afterward both were able to describe all that had occurred. The electroencephalograms of both patients revealed no change during any of the attacks. This observation is in accord with the findings of Hess (1949), who noted no change in the electroencephalogram during cataplectic attacks. In one patient we have had the opportunity to record an episode of sleep paralysis. During this episode the patient appeared in a state rather similar to a cataplectic attack. The patient was able to move his eyes but was unable to speak, although faint movements of the lips were observable. All four extremities were apparently paralyzed and the deep reflexes were depressed during the attack. Following the attack the reflexes became normal, and the patient showed no residual symptoms. The patient recalled all that had occurred during the episode although he had been unable to respond. The electroencephalogram during this episode showed no abnormalities; during parts of the episode the record showed patterns resembling those seen in other narcoleptic patients during drowsiness. The findings in this patient are the same as those reported by Pond (1952), who recorded what he regarded as an episode of sleep paralysis. He likewise felt that the electroencephalogram showed no abnormal change during the attack. Janzen and Behnsen (1940) probably recorded an attack of sleep paralysis.

COMMENT

The observations in this group of patients permit several conclusions. The basal or alert electroencephalogram in these patients reveal no significant abnormalities and conforms to what would be anticipated in a controll group of patients without neurologic disease. The present study is based on a sufficiently large group that we can make the generalization that no significant abnormality exists in the resting records of narcoleptic patients. This confirms the findings of both Blake, Gerard and Kleitman (1939) and of Dynes and Finley (1941). Persistent drowsiness characterizes these patients. This occurs early in the course of the examination but only rarely passes over into the stages of light sleep. The drowsiness is a physiologic state, and the electroencephalograms resemble those seen in normal persons during the so-called ''floating'' or drowsy stage.

The fact that the narcoleptic patient can remain in a drowsy state for periods of up to a half hour or more raises some points of interest with regard to the pathophysiology of narcolepsy. Most authors emphasize that the narcoleptic attack is a sudden episode of irresistible sleep. This apparent paroxysmal seizure of sleep has led Wilson (1928) to relate narcolepsy to the epileptic disorders. However, our observations lead us to an alternate conclusion: namely, that the narcoleptic patient is chronically in a state of drowsiness. The patient, so to speak, continously verges on sleep, so that when sleep finally occurs it is neither sudden nor unexpected. Narcolepsy, then, is a disease characterized by persistent impairment of the

normal alert state and not basically related to the epileptiform disorders. The etiology of narcolepsy is not clarified by this study save that the findings of normal electroencephalograms in this large group of patients suggest that no significant structural alteration of the brain has occurred. This opinion is supported by the clinical observations on these patients, which indicate no evidence of organic brain changes.

When sleep itself occurs, the state usually regarded as the narcoleptic attack proper, the electroencephalogram reveals only normal sleep patterns. During the occurrence of the other elements of the tetrad, namely during cataplectic attacks and sleep paralysis, there are no abnormalities of the electroencephalogram. These findings further corroborate the conclusion that narcolepsy is a disease sui generis and not related to the convulsive disorders.

Although the cause of narcolepsy has been unknown, the pathophysiology of narcolepsy has traditionally been assumed to be the consequence of disturbed function in the hypothalamus, the classic ''sleep-center''. In more recent years Magoun and co-workers (French, von Amerongen and Magoun 1952) have demonstrated the existence of a brain-stem reticular system stimulation of which is associated with ''activation'' of the electroencephalogram and arousal of the animal. Conversely, lesions in this system are associated with clinical signs of unresponsiveness and coma (French and Magoun 1952). More recently, French, Verzeano and Magoun (1953) have shown that ethyl ether and barbiturates selectively block the transmission of afferent impulses in the medial conduction systems, while leaving unimpeded those in the lateral (lemniscal) systems. The fact that the electroencephalograms of our patients were normal in the alert state and showed normal patterns during drowsiness and sleep suggests that the basic disorder may be a reversible physiologic disturbance in the reticular activating system.

SUMMARY

One hundred patients with the clinical diagnosis of narcolepsy were examined electroencephalographically. The basal or alert electroencephalograms were found to be within normal limits. Drowsiness beginning within the first 4 min. of the recording occurred in the majority of patients. Almost all patients manifested drowsiness at some time during the recording. Sustained drowsiness lasting for periods up to 30 min. was characteristic of these patients. Opening and closing the eyes, counting, hyperventilation and photic stimulation, measures which alert the normal patient, were commonly ineffective in narcoleptics. In spite of persistent drowsiness, actual sleep was uncommon under the circumstances in which the recordings were made. Electroencephalograms made during cataplectic attacks and an attack of sleep paralysis were normal. The implications of these findings are discussed.

REFERENCES

AIRD, R. B., GORDON, N. S. and GREGG, H. C. Use of phenacemide (Phenurone) in treatment of narcolepsy and cataplexy: A preliminary report. *A.M.A. Arch. Neurol. Psychiat.*, **1953**, *70*: 510-515.

BLAKE, HELEN, GERARD, R. W. and KLEITMAN, N. Factors influencing brain potentials during sleep. *J. Neurophysiol.*, **1939**, *2*: 48-60.

COHN, ROBERT and CRUVANT, B. A. Relation of narcolepsy to the epilepsies: A clinical-electroencephalographic study. *Arch. Neurol. Psychiat.*, Chicago, **1944**, *51*: 163-170.

DAVIS, H., DAVIS, P. A., LOOMIS, A. L., HARVEY, E. N. and HOBART, G. Human brain potentials during the onset of sleep. *J. Neurophysiol.*, **1938**, *1*: 24-38.

DYNES, J. B. and FINLEY, K. H. The electroencephalograph as an aid in the study of narcolepsy. *Arch. Neurol. Psychiat.*, Chicago, **1941**, *46*: 598-612.

FRENCH, J. D. and MAGOUN, H. W. Effects of chronic lesions in cerebral cephalic brain stem of monkeys. *A.M.A. Arch. Neurol. Psychiat.*, **1952**, *68*: 591-604.

FRENCH, J. D., VERZEANO, M. and MAGOUN, H. W. A neural basis for the anesthetic state. *A.M.A. Arch. Neurol. Psychiat.*, **1953**, *69*: 519-529.

FRENCH, J. D., VON AMERONGEN, F. K. and MAGOUN, H. W. An activating system in the brain stem of the monkey. *A.M.A. Arch. Neurol. Psychiat.*, **1952**, *68*: 577-590.

GIBBS, F. A. and GIBBS, ERNA L. *Atlas of Electroencephalography.* Vol. 1, Methodology and Controls, 327 pp.; vol. 2, Epilepsy, 422 pp. Ed. 2, Cambridge, Mass., Addison-Wesley Press, **1950**.

HESS, RUDOLF. Elektrencephalographische Beobachtungen beim kataplektischen Anfall. *Arch. Psychiat.*, **1949**, *183*: 132-141.

JANZEN, R. and BEHNSEN, G. Beitrag zur Pathophysiologie des Anfallsgeschehens, insbesondere des kataplektischen Anfalls beim Narkolepsiesyndrom: Klinische und hirnbioelektrische Untersuchung. *Arch. Psychiat.*, **1940**, *111*: 178-189.

MURPHY, W. F. Narcolepsy: A review and presentation of seven cases. *Amer. J. Psychiat.*, **1941**, *98*: 334-339.

POND, D. A. Narcolepsy: A brief critical review and study of eight cases. *J. Ment. Sc.*, **1952**, *98*: 595-604.

ROTH, NATHAN. Problems in narcolepsy. *Bull. Menninger Clin.*, **1946**, *10*: 160-170.

STOUPEL, M. N. Etude électroencéphalographique de sept cas de narcolepsie - cataplexie. *Rev. neurol.*, **1950**, *83*: 563-570.

WILSON, S. A. K. The narcolepsies. *Brain*, **1928**, *51*: 63-109.

Reference: DALY, D. D. and Yoss, R. E. Electroencephalogram in narcolepsy. *EEG Clin. Neurophysiol.*, **1957**, *9*: 109-120.

ANNOUNCEMENT

ASSOCIATION FOR RESEARCH IN NERVOUS AND MENTAL DISEASE

At the Thirty -Sixth Annual Meeting of the Association for Research in Nervous and Mental Disease held in New York City on December 7 and 8, 1956, the following officers were elected for the year 1957.

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The Thirty-Seventh Annual Meeting will be held at the Hotel Roosevelt in New York City on December 13 and 14, 1957. The topic will be "The Effect of Pharmacologic Agents on the Nervous System".

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THE ONTOGENETIC DEVELOPMENT OF STEADY POTENTIAL DIFFERENCES IN THE CEREBRAL CORTEX IN ANIMALS [1]

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INTRODUCTION

Steady potential differences are one of the best known electrical manifestations of living matter. Potential differences between tendon and muscle in animals, between roots and leaves in plants, currents of injury, etc. have been thoroughly investigated for over a century. Steady potentials have also been found in the CNS. Further research in this direction was checked, however, by the invention of simple apparatus which made it easier to record rapid electrical manifestations of nervous activity — action potentials and the EEG.

Only in recent years have investigations of this old problem again been widely resumed. The cortical surface of mammalian brain is positive to other parts of the nervous system (sciatic nerve, cerebral ventricles) by approximately 10-20 mV. as was shown by Burr and Harman (1939) for rat, by Goldring, Ulett, O'Leary and Greditzer (1950) for monkey and man, by Goldring and O'Leary (1951) for rabbit, by Goldensohn, Schoenfeld and Hoefer (1951) for dog and by Kempinsky (1954) for cat. Changes in this potential difference may be elicited by a number of different physiological and pathological states. The most striking changes of cortical polarity were obtained with anoxia. After some minutes of anoxia the cerebral cortex becomes negative (Leão 1947; Goldensohn, Schoenfeld and Hoefer 1951; van Harreveld and Stamm 1953b). Smaller and less regular changes of cortical potential accompany convulsive EEG activity (Goldring, Ulett, O'Leary and Greditzer 1950; Goldring and O'Leary 1951; van Harreveld and Stamm 1954b), local occlusion of cerebral arteries (Kempinsky 1954), local application of some drugs on the cortical surface (e.g. malononitrile — Goldring, O'Leary and Lam 1953; Veratrine — Goldring and O'Leary 1954).

Changes of cortical polarity are probably a major factor in Leão's spreading depression of EEG as was shown for the first time by Leão (1947).

Nevertheless little is understood so far about the intimate nature of cortical polarisation, about its anatomical and metabolic basis, its physiological significance, its relation to EEG and other manifestations of cortical activity. An ontogenetic approach may prove of value in helping to solve these problems.

A steady potential difference between the cortical surface and a reference point may be due to regular orientation of cortical nervous cells and to a certain distribution of electrical potentials on these cells. It is possible, then, to consider the steady potential of cerebral cortex as the average of individual potentials of single cortical neurons, as was suggested for other electrically polar tissues by Lund (1928).

If this assumption be correct, cortical polarisation should develop during ontogenesis according to the functional and morphogenetic development of the cerebral cortex. The purpose of this paper is to verify this hypothesis.

TECHNIQUE

All experiments were carried out on animals lightly anesthetised with Dial.

Calomel cell electrodes with 0,9 per cent NaCl as the salt bridge and in the electrode vessels were used to record the steady potentials. Cotton thread was used to make contact with the cortex exposed by trephine holes (5 mm. in diameter), situated over the pa-

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rietal areas of both hemispheres. A potentiometer placed in series with the electrodes served to balance the initial voltage. The potential differences were amplified by a differential directly coupled amplifier and registered by a voltmeter. To exclude inaccuracies produced by variations in the base-line of the D-C amplifier the potentials were measured not against zero but by operating a changeover switch against the reversely connected electrodes. The value of the potential was measured twice in this way. In exact measurements of absolute values of potentials the potential difference was determined with electrodes in one position (e.g. electrode A on cerebral cortex, electrode B on the sciatic nerve) and immediately afterwards the electrodes were interchanged (electrode A on the sciatic nerve and electrode B on the cortex) and a new determination was made. By this simple method other sources of error (temperature differences, grid currents) can be easily excluded because all potentials originating outside the animal will give zero after subtracting the values obtained with the first position of electrodes from the values obtained with the second one (Burr 1944).

For recording slow potential changes the chopper technique described by Goldring and O'Leary (1951) was used. A switch placed across the input of an EEG channel, short-circuited the input for one second and connected it to electrodes for a further 200 msec. Steady and slowly changing differences can be directly recorded by this method as square waves in one of the EEG channels. Smooth curves were then redrawn from the original chopper traces. The EEG was recorded with a six-channel EEG apparatus (Ediswan) with the aid of steel needles plunged directly into the exposed bone of the skull. Bipolar recording was used throughout.

When attempting to determine steady potentials it is of prime importance where and between which points the measurements should be made. Similar changes of potential difference between A and B may be obtained by a certain change of electrical potential at point A or by an opposite change of potential at B, or by changes of potential at both A and B. For precise determinations of the slow potential change in a cortical area, it is important to place the reference electrode on a point, the potential of which will not change in the course of the experiment.

In papers dealing with the measurement of steady potential differences in CNS various reference points have been used, e.g. the uninjured surface of peripheral nerve trunks (sciatic nerve — Burge *et al.* 1936; Burr and Harman 1939; Goldensohn, Schoenfeld and Hoefer 1951), the bones of the skull or a remote area of brain surface (Marshall, Essig and Dubroff 1951; van Harreveld 1946), the pinna (van Harreveld and Stamm 1954), the cut surface of the brain (Hobbiger and Werner 1948) or the cerebral ventricles (Libet and Gerard 1941; Goldring and O'Leary 1951).

It is difficult to decide which of these positions for the reference electrode should give the best results. For determination of correct absolute values of potential differences careful comparison of results obtained by different methods is essential. In the experiments described here four different methods were used throughout.

1. Registration of potential difference between the cortex and the sciatic nerve. This method interferes very little with functions of the nervous system. However, potentials of extracortical provenance may be registered. The exclusively cortical origin of potentials measured in this way is therefore doubtful.

2. Determination of the potential difference between a cortical area damaged by thermocoagulation and the normal cortical surface of the contralateral hemisphere. The cortical origin of potential difference measured in this way is evident.

3. Determination of cortical depolarisation caused by arrest of brain circulation. The animals were killed by decapitation and the potential difference as in (2) was registered in the isolated head for the next 20 min. The EEG is completely suppressed in similar conditions in 10-20 sec. On the other hand, cortical polarity remains almost unchanged for 2-5 min., as was demonstrated by Leão in 1947. Only then does rapid cortical depolarisation begin (fig. 1) and is nearly complete after 10-15 min. Depolarisation of the cerebral cortex attained in the course of 20 min. after death was determined by subtracting the ter-

minal potential difference from the original one. The metabolic character of this slow potential change makes the values obtained by this method especially reliable. Assuming that the potential of the damaged area does not change after death, changes in the normal cortex may be considered as the source of this slow depolarisation. There is, however, a technical disadvantage in the very slow depolarisation rate 10 min. or later after death. Depolarisation is not quite complete even after 20 min. This slightly decreases the precision of these observations.

4. Determination of the potential differences between a cortical area damaged by thermocoagulation and the normal cortical surface in an animal dead for 20 min. In dead rats already used for determination (2) and (3) another cortical area was destroyed by thermocoagulation. The potential difference obtained in this way should theoretically be the potential difference of (2) minus the potential difference of (3). This last technique demonstrates together with (2) and (3) the biologic character of cortical polarity revealed by thermocoagulation.

RESULTS

(a) *Ontogenetic development of cortical steady potential in rats.*

Most experiments were carried out on rats aged 5, 10, 15, 20 and 90 days. Light Dial anesthesia was used throughout and the body temperature was kept above 30°C during the whole experiment.

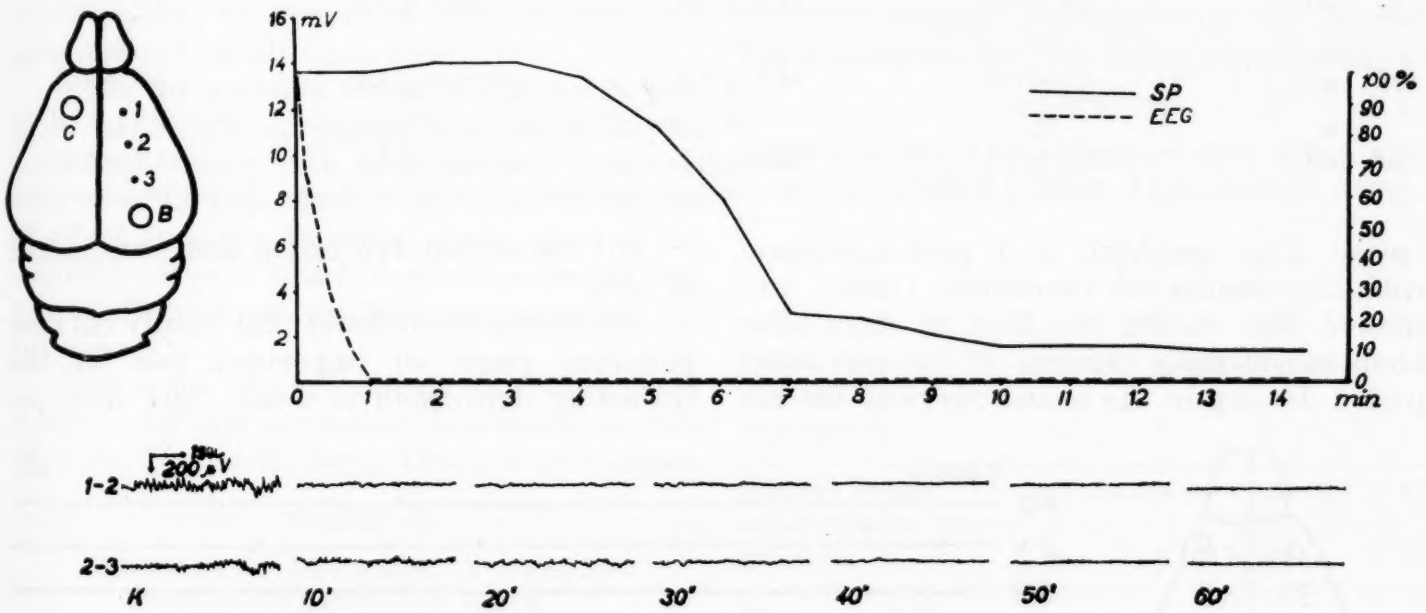

Fig. 1

Determination of injury potential and terminal depolarisation in the cerebral cortex of the rat.
Diagram of the brain:
C — cortical area destroyed by thermocoagulation
B — normal cortical surface
1, 2, 3 — steel needle electrodes fixed in skull bones.
EEG record: K — control tracing. In further tracings the timing is from the circulatory arrest in seconds.
The graph gives values of EEG changes in per cent of initial amplitude and slow change of the initial potential difference between C and B in mV. (ordinate). On the abscissa — time from circulatory arrest in minutes.

When the operative procedure (2 trephine holes 5 mm. in diameter above both parietal areas, and preparation of the sciatic nerve) was completed the technical methods already described were used to determine the steady cortical potential. The results of these experiments are given in table I; they show, that there is a consistent relation between the magnitude of cortical steady potential and age. The four technical methods all gave similar results. Slightly different values obtained by method (1) may be due to ontogenetic development of the sciatic nerve po-

TABLE I

ONTOGENESIS OF CORTICAL POTENTIAL IN RAT DETERMINED BY 4 DIFFERENT METHODS

Age in days		*Method used (See text)*			
		1	*2*	*3*	*4*
5	n	18	9	8	8
	mV.	1.3 ± 0.3	2.6 ± 0.4	— 1.0 ± 0.2	— 2.0 ± 0.4
10	n	21	10	10	6
	mV.	4.9 ± 0.3	6.0 ± 0.7	— 4.2 ± 0.8	— 2.8 ± 0.4
15	n	20	10	10	10
	mV.	6.0 ± 0.2	11.2 ± 0.6	— 10.7 ± 0.6	— 2.4 ± 0.1
20	n	20	7	7	7
	mV.	6.7 ± 0.6	14.0 ± 0.9	— 12.4 ± 1.0	— 2.8 ± 0.2
D	n	12	17	8	14
	mV.	20.6 ± 1.1	19.0 ± 0.8	— 16.7 ± 1.7	— 3.7 ± 0.6

tential. This possibility is in good agreement with the results of Oganisian (1948) who showed that during the first 20 days after birth considerable changes of the refractory period develop in the sciatic nerve of the rat.

(b) *Spreading depression and ontogenesis of rats.*

There can be no doubt that steady cortical potential plays an important role in the spreading depression of Leão. The slow po-

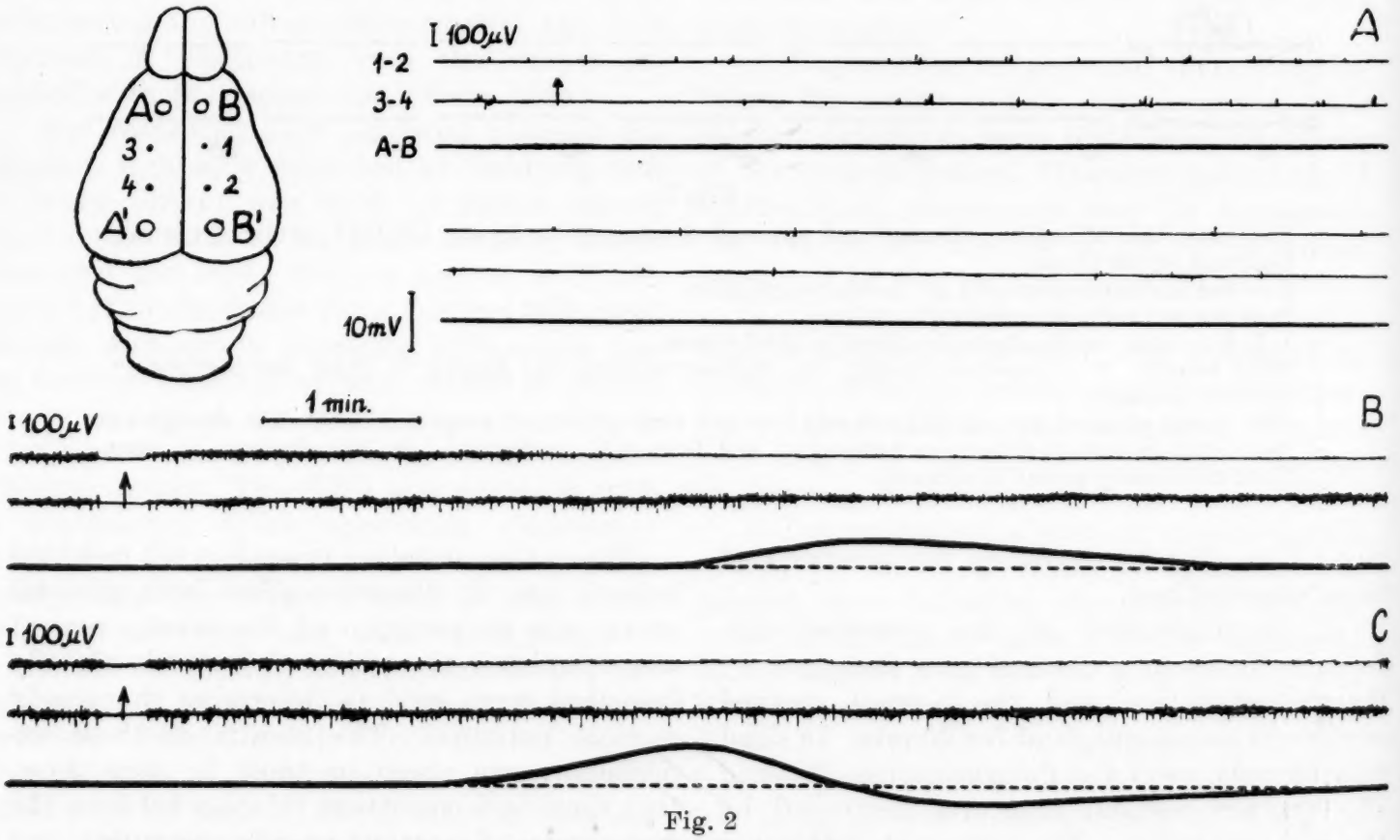

Fig. 2

Spreading depression in 10 (A), 15 (B) and 20 (C) day old rats.
1-2, 3-4: electrical cortical activity recorded with steel needle electrodes.
A - B: slow potential change recorded with calomel cell electrodes between A and B. An upward deflection indicates increased negativity of A.
The arrow indicates application of 1 per cent KCl solution on area A in all records.
Calibration: 100 μV. for EEG, 10 mV. for record of slow potential change.

tential change accompanying the wave of EEG depression may be interpreted as reversible diminution of transcortical polarisation. Van Harreveld and Stamm (1953a) have reported that the presence of spontaneous EEG activity is not a necessary condition for initiating spreading depression. In spite of the complete absence of spontaneous EEG activity in rabbits in deep pentobarbital anesthesia, the slow potential change of spreading depression remained unchanged and the propagation velocity was decreased only insignificantly as compared with animals not anesthetised at all.

Thus the question arises, whether it is possible to initiate spreading depression in the cortex of young rats with cortical polarisation considerably smaller than in the brains of adult animals. In other words, what is the smallest value of steady cortical potential still consistent with production of spreading depression ?

In a series of experiments an attempt was made to initiate spreading depression in rats aged 10, 15 and 20 days. One per cent potassium chloride solutions on filter paper strips 2 x 2 mm. were used for stimulation. Figure 2 illustrates records characteristic for various age groups and table II gives the average values resulting from these experiments.

TABLE II

SPREADING DEPRESSION DURING ONTOGENESIS OF RATS

Age in days	*10*	*15*	*20*	*Adult*
n	9	12	9	10
depression	0	7	9	10
no depression	9	5	0	0
per cent of depressions	0	58.4	100	100
maximal negativity (mV.)		3.9 ± 0.7	3.4 ± 0.6	6.4 ± 0.9
duration of the rising phase of the slow potential change (sec.)		94″ ± 6″	68″ ± 9″	64″ ± 6″

In rats 10 days old, in which the steady cortical potential is less than one third of the cortical polarisation in adult animals it was not possible to initiate spreading depression although 10 per cent KC1 was used for stimulation in some experiments. In rats aged 15 days it was possible to obtain spreading depression with 1 per cent KC1 in most experiments, but the reaction was still unstable and irregular. Only in 20 day old rats does spreading depression develop as regularly as in adult animals. The amplitude of the slow potential change accompanying the spreading depression does not differ significantly in the 15 and 20 days old groups. In both these groups, however, the maximum negativity is considerably smaller than in adult animals ($P = 0.01$). Duration of the slow potential change (from the beginning to maximum of negativity) is reduced significantly between the 15th and 20th day of age. Later no gross change in the time course of the slow potential was observed.

TABLE III

CORTICAL POLARISATION IN NEW BORN AND ADULT GUINEA PIGS AND ADULT RATS

		New born guinea-pig	*Adult guinea-pig*	*Adult rat*
Cortical injury potential (See technique 2)	mV.	11.0 ± 0.5	15	19.0 ± 0.8
	n	7	1	17
Cortical anemic depolarisation (See technique 3)	mV.	10.3 ± 0.7	12.5	16.7 ± 1.7
	n	6	1	8
Maximum of the negative potential change accompanying spreading depression	mV.	5.4 ± 0.2	6.5	6.7 ± 0.5
	n	11	2	40

(c) *Cortical polarity and spreading depression in new-born guinea-pigs.*

The gestation period of guinea-pigs is almost twice as long as in rats. Guinea-pigs are born with a CNS much more developed from both the morphological and functional point of view than rats. Cortical polarisation was therefore determined in a group of new-born

guinea-pigs using methods (2) and (3). The possibility of initiating spreading depression with application of 1 or 2 per cent KC1 was also examined in the same animals.

Values given in table III were obtained from this experimental series. Figure 3 shows a typical record of spreading depression taken from such an experiment. It follows from these results that a new-born guinea-pig has a well developed cortical steady potential and that spreading depression may be elicited in guinea-pigs from the first day of life by direct stimulation of the cerebral cortex with KC1.

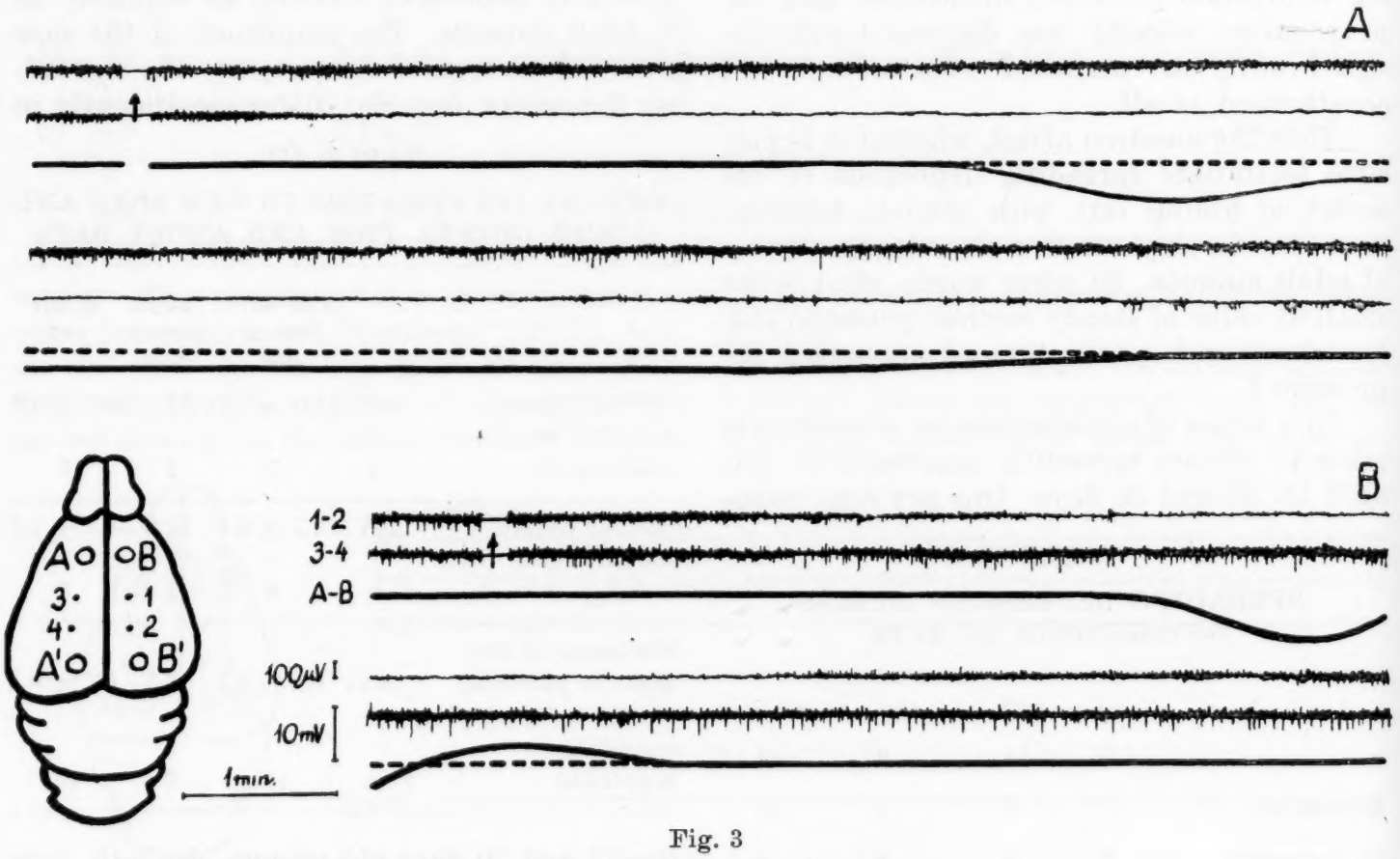

Fig. 3

Spreading depression in new born (A) and adult (B) guinea-pig.
Upper 2 lines — electrical cortical activity, recorded with steel needle electrodes 1, 2 (in upper tracing) and 3, 4 (in lower tracing).
Continuous line — record of slow potential change, recorded with calomel cell electrodes between A and B. An upward-deflection indicates increased negativity of A.
The arrow indicates application of 1 per cent KCl in both records.
Calibration: 100 μV. for EEG, 10 mV. for slow potential change record.

DISCUSSION

In these experiments a clear pattern of development of cortical polarity during the ontogenesis of rat was demonstrated. It is important to note, however, that this steady potential difference develops in a complex, multilayer cellular system, individual elements of which may be of different and even of opposite polarity and that the potential measured in the whole cortex is an average vale only. This hypothesis was put forward by Bishop and O'Leary (1950) on the basis of changes in sensory primary responses, brought about by polarisation of the cerebral cortex. More recently Sutin and Campbell (1955) have shown that the steady potential difference across the simple unilaminar cortex of the cornu Ammonis is greater than the steady potential difference across the isocortex.

The composite average character of the cortical steady potential makes the interpretation of ontogenetic data rather difficult, as it is this average cortical polarity that has been studied. It must, therefore, not be forgotten that the ontogenetic development of cortical polarity is due not only to the de-

velopment of polarity of individual neuronal elements but also to the development of regular cytoarchitectonics, of regular orientation of these cells, this being another necessary condition for the polarisation of the whole cortex.

The greatest absolute increment of cortical polarisation was found between the 10th and 15th day of age, the greatest relative increment in the period from the 5th to the 10th day. The relative increment becomes smaller thereafter, in agreement with the conditions of development of a limited cellular population of the cerebral cortex. The magnitude of the cortical potential does not depend upon the weight of the brain (table IV), as there is a gross difference between the course of development of these two values in rats (weight data after Suitsu 1920). Measurements carried out in adult mice, whose brain is lighter than the brain of new-born rats, have also shown that there is no relation between the weight of the brain and the cortical steady potential, which attains 15.9 ± 0.7 mV. in mice.

Comparison of the ontogenetic development of cortical polarisation with biochemical and morphological data may prove of prime importance. According to Sugita (1917, 1918a, b) the thickness of the cerebral cortex in rat increases until the 10th day of life. Other values indicating the morphological development of cerebral cortex also become stabilised at this age (table IV). It appears, therefore, that in addition to the thickness of cerebral cortex and the number and size of neuronal elements there are other factors essential for the cortical potential. After the morphological development of the cortex is practically complete biochemical changes are responsible for the further increase of cortical polarisation. The greatest decrease of water content of the brain occurs between the 10th and 20th day of age (Donaldson 1924, table IV). According to Bieth, Mandel and Revel (1952) the amount of desoxypentosonucleic acid found in chromosomes of the brain cells increases until the period of cell division is completed. This occurs in rat brain about the 16th day of postnatal life. The biochemical development of brain is by no means complete at this period as there are only 31.6 per cent of lipids and 50 per cent of nitrogen as compared with the values in adult animals. These results are in good agreement with those of earlier workers who investigated rat

TABLE IV

COMPARISON OF VARIOUS MORPHOLOGICAL DATA WITH THE DEVELOPMENT OF CORTICAL STEADY POTENTIAL IN THE ONTOGENESIS OF RATS

Author	*Subject studied*		*Age in days*						
			1	*2*	*10*	*15*	*20*	*30*	*90*
Suitsu 1920	weight of the brain	g	0.217	0.509	0.947	1.057	1.150	1.311	1.791
Sugita 1917	thickness of cerebral cortex	mm	0.74	1.25	1.73	1.76	1.84	1.84	1.94
Sugita 1918a	volume of cerebral cortex	mm^3	35.97	111.46	240.02	255.94	288.93	314.03	397.96
Sugita 1918a	total number of cells in cerebral cortex as compared with new born rats	%	100	165	192	191	202	208	207
Sugita 1918b	Size of cells:								
	in lamina pyramidalis	μ	12.9	18.2	22.8	23.7	23.6	23.9	22.7
	in lamina ganglionaris	μ	18.9	24.9	30.8	31.3	31.2	31.4	32.8
Donaldson 1924	water contents of brain	%	88.0	87.8	86.7	84.6	82.8	80.3	78.6
Bures 1955	cortical steady potential	mV.		2.6	6.0	11.9	14.0		19.0

brains for phosphatides (Koch and Koch 1913) and fatty acids (Waelsch, Sperry and Stoyanoff 1941) and found a rather steep increase of these substances between the 10th and 40th day of age.

In recent years investigations of the acid-soluble phosphate fraction in rat brain during ontogenesis have been made by Bieth, Mandel and Weill (1953). CP and ATP significantly increase after the 10th day of age. Also the ATP-ase activity distinctly increases up to the 14th day of age (Nikitin and Golubitskaya 1954; Křeček and Stěpánek 1953).

A number of papers deals with the development of brain O_2 consumption in infant rats (Himwich, Sykowski and Fazekas 1941; Tyler and van Harreveld 1942; Mysliveček and Jílek 1953; Hahn, Koldovsky, Křeček and Křečková 1954; Weill and Mandel 1953). Although there are some discrepancies in details, all these workers confirm a great increase of brain Qo_2 between the 10th and 20th day. The results of Himwich and co-workers (1942), who found that the effect of potassium on Qo_2 of brain slices is minimal in new-born rats, are of great importance. During the first 20 days of life there appears in brain slices the ability to respond to increased KC1 concentration in the medium with increased O_2 uptake, which is approximately the same as in adult rats.

Experiments on spreading depression also illustrate that the development of rat brain continues after the 20th day of life. There is a clear-cut difference between 20 days old rats and adult animals as far as the amplitude of the slow potential wave accompanying the spreading depression is concerned, an even more pronounced difference than that seen in the cortical steady potential. It appears that up to the 10th day of life the cortical steady potential does not originate in those cortical elements which are responsible for the production of spreading depression. In rats aged 15 days spreading depression appears in some brains for the first time. This is in agreement with other papers dealing with ontogenesis of functions of the rats CNS. During the period from 10th to 15th day there appear EEG (Crain 1952) and sensory primary responses to acoustic stimuli (Bureš 1953). This coincidence suggests that nervous structures of the cerebral cortex, whose maturation is a condition for the appearance of EEG activity and sensory primary responses, are identical with those responsible for the increase of cortical polarisation after the 10th day of life. This increase has no direct correlation with morphogenetic development, which becomes distinctly stabilised after the 10th day of life. Nevertheless a recent study of van Harreveld and Stamm (1954a) makes it likely that this increase depends upon certain — from the morphological point of view rather unimpressive — changes in cortical neurons. According to this paper, it is impossible to obtain a spreading depression in rabbits after long lasting asphyxiation of rostral parts of the brain, causing the destruction of most cortical neurons. There can, therefore, be no doubt that the phenomenon of Leão is connected with the activity of neurons and not of other cortical elements. The increase of cortical steady potential between the 10th and 20th day may be a result of some changes in neuronal metabolism in this period.

Although we cannot as yet determine exactly the metabolic and structural basis of cortical polarisation, it follows from our experiments that the cortical steady potential may be taken as an index of functional maturity of the cerebral cortex. Especially the results obtained in new-born guinea-pigs agree very convincingly with other experimental data, confirming maturation of the cerebral cortex in guinea-pigs during intrauterine life (Kimel and Kavaler 1951). The largest absolute increment of cortical polarity between the 10th and 15th day in rats precedes a number of functional changes occuring about this time (changes in thermo-regulation and water metabolism — Hahn 1953, Koldovsky *et al.* 1953; development of cortical postural reflexes — Tang 1935, Brooks and Peck 1940; beginning of sound-induced seizures — Bureš 1953, etc.). Whether this high cortical polarisation is essential for normal function of cerebral cortex remains to be seen.

SUMMARY

Steady potential differences of cerebral cortex in rats and guinea-pigs were measured

during ontogenesis and the possibility of eliciting a spreading depression by topical application of KC1 to the cortical surface in animals of various ages was studied.

Cortical steady potential was measured using four different methods:

1. Potential difference between the sciatic nerve and cerebral cortex.

2. Potential difference between a damaged cortical area and normal cortical surface (cortical injury potential).

3. Terminal depolarisation — negative potential shift developing in cerebral cortex during the 20 min. after total circulatory arrest.

4. Potential difference between normal cortical surface and a cortical area damaged 20 min. after death.

The cortical surface of adult rats is 19-20 mV. positive against other electricaly indifferent areas. This positive potential mainly develops during the first 20 days of life in rats, being 2.6 mV. in rats aged 5 and 14.0 mV. in rats aged 20 days.

Only after the age of 15 days it is possible to elicit spreading depression by topical application of 1 per cent KCl in rats. The slow potential change accompanying the wave of EEG depression is smaller in amplitude and more prolonged in duration in the 15 day old rats than in adult animals.

Guinea-pigs on the contrary display definite cortical polarisation from just after birth. New-born guinea-pigs generally respond by a spreading depression to topical application of 1 per cent KCl to the cortical surface.

The values of cortical polarisation in different age groups are compared with other data concerning the morphogenetic and functional development of the brain in rats.

I should like to express my thanks to Miss Vlasta Kaiserová for her assistance throughout this study.

REFERENCES

Bieth, R., Mandel, B. et Revel, J. P. Etude biochimique sur le rythme de croissance du cerveau chez quelques espèces de mammifères. *J. Physiol.*, **1952**, *44*: 214.

Bieth, R., Mandel, P. et Weill, J. D. Evolution des composés phosphorés acido-solubles au cours du développement du cerveau chez le rat. *C. R. Soc. Biol.*, **1953**, *147*: 1273-1276.

Bishop, G. H. and O'Leary, J. L. The effect of polarizing currents on cell potentials and their significance in the interpretation of central nervous system activity. *EEG Clin. Neurophysiol.*, **1950**, *2*: 401-416.

Brooks, M. C. Ch. and Peck, M. E. Effect of various cortical lesions on development of placing and hopping reactions in rats. *J. Neurophysiol.*, **1940**, *3*: 66-73.

Bures, J. Susceptibility to convulsions in reflex epilepsy in the ontogenesis of rats and mice. *Physiol. Bohemosl.*, **1953**, *2*: 274-283.

Burge, W. E., Wickwire, G. C., Orth, O. S., Neild, H. W. and Elhardt, W. P. A study of the electrical potential of the cerebral cortex in relation to anesthesia, consciousness and unconsciousness. *Amer. J. Physiol.*, **1936**, *116*: 19-20.

Burr, H. S. Variables in DC measurement. *Yale J. Biol. Med.*, **1944**, *17*: 465-478.

Burr, H. S. and Harmann, P. J. Jr. Voltage gradients in the nervous system. *Trans. Amer. Neurol. Ass.*, **1939**, *65*: 11-14.

Crain, S. M. Development of electrical activity in the cerebral cortex of the albino rat. *Proc. Soc. Biol. Med.*, **1952**, *81*: 49-51.

Donaldson, H. U. *The Rat.* Philadelphia, The Wistar Institute. **1924**.

Goldensohn, E. S., Schoenfeld, R. L. and Hoefer, P. F. A. The slowly changing voltage of the brain and the electrocorticogram. *EEG Clin. Neurophysiol.*, **1951**, *3*: 231-236.

Goldring, S. and O'Leary, J. L. Experimentally derived correlates between EEG and steady cortical potential. *J. Neurophysiol.*, **1951**, *14*: 275-288.

Goldring, S. and O'Leary, J. L. Correlation between steady transcortical potential and evoked response. I. Alterations in somatic receiving area induced by Veratrine, Strychnin, KCl and Novocaine. *EEG Clin. Neurophysiol.*, **1954**, *6*: 189-212.

Goldring, S., O'Leary, J. L. and Lam, R. L. Effect of malononitrile upon the electrocorticogram of the rabbit. *EEG Clin. Neurophysiol.*, **1953**, *5*: 395-400.

Goldring, S., Ulett, G., O'Leary, J. and Greditzer, A. Initial survey of slow potential changes obtained under resting conditions and incident to convulsive therapy. *EEG Clin. Neurophysiol.*, **1950**, *2*: 297-308.

Hahn, P. Izmenenije v potreblenii kisloroda krysami v tecenie ich postnatalnogo razvitija i zavisimost etich izmenenij ot temperatury okruzajuscej sredy. *Physiol. Bohemosl.*, **1953**, *2*: 373-387.

Hahn, P., Koldovsky, O., Krecek, J. und Kreckova, J. K voprosu o razvitii aerobnogo metabolizma v mozgach molodych krys. *Physiol. Bohemosl.*, **1953**, *2*: 171-177.

Himwich, H. E., Bernstein, A. O., Fazekas, J. F., Herrlich, H. C. and Rich, E. The metabolic effects of potassium, temperature, methylene blue and paraphylendiamine on infant and adult brain. *Amer. J. Physiol.*, **1942**, *137*: 327-330.

Himwich, H. S., Sykowski, P. and Fazekas, J. F. A comparative study of excised cerebral tissues of adult and infant rats. *Amer. J. Physiol.*, **1941**, *132*: 293-296.

HOBBIGER, F. und WERNER, G. Ueber den Einfluss physikalischer und chemischer Narkosen auf Acetylcholingehalt und Ruhepotential des Zentralnervensystems von Kaltblütern. *Arch. int. Pharmacodyn.*, **1948**, *76*: 229-241.

KEMPINSKY, W. H. Steady potential gradients in experimental cerebral vascular occlusion. *EEG Clin. Neurophysiol.*, **1954**, *6*: 375-388.

KIMEL, V. M. and KAVALER, F. Biochemical and physiological differentiation during morphogenesis. XIII. Functional maturation of the motor cortex of the foetal guinea-pig as judged by the appearance of muscular responses to electrical stimulation of the cortex. *J. comp. Neurol.*, **1951**, *94*: 257-265.

KOCH, W. and KOCH, M. L. Contributions to the chemical differentiation of the central nervous system. III: The chemical differentiation of the brain of albino rat during growth. *J. Biol. Chem.*, **1913**, *15*: 423.

KOLDOVSKY, O., KRECEK, J., KRECKOVA, J. and MIKULAS, I. The influence of rearing in the dark on the development of water metabolism in young rats. *Physiol. Bohemosl.*, **1953**, *2*: 367-372.

KRECEK, J. und STEPANEK, F. Fosfatnyj energeticeskij metabolism v mozgach molodych krys. *Physiol. Bohemosl.*, **1953**, *2*: 297-302.

LEÃO, A. A. P. Further observations on the spreading depression of activity in the cerebral cortex. *J. Neurophysiol.*, **1947**, *10*: 409-414.

LEÃO, A. A. P. and MORISON, R. S. Propagation of spreading cortical depression. *J. Neurophysiol.*, **1945**, *8*: 33-45.

LIBET, B. and GERARD, R. W. Steady potential fields and neurone activity. *J. Neurophysiol.*, **1941**, *4*: 438-455.

LUND, E. A. Relation between continuous bio-electric currents and cell respiration II. *J. exp. Zool.*, **1928**, *51*: 265-290.

MARSHALL, W. H., ESSIG, C. F. and DUBROFF, S. J. Relation of temperature of cerebral cortex to spreading depression of Leão. *J. Neurophysiol.*, **1951**, *14*: 153-166.

MYSLIVECEK, J. und JILEK, L. Razvitie potreblenija kisloroda v nekotorych tkanjach krysy. *Physiol. Bohemosl.*, **1953**, *2*: 363-366.

NIKITIN, B. N. und GOLUBITSKAYA, P. N. Vozrastnyje izmenenija v adenosintrifosfataznoj aktivnosti tkani mozga. *Uc. zapiski Chark. univ., Tr. In. Biol.*, **1951**, *21*: 143-151.

OGANISJAN, A. A. Tetanizirovannoje odinocnoje sokrascenije kak pokazatel funkcionalnogo sostojanija nervno-mysecnogo apparata v ontogeneze. *Fiziol. zurn. SSSR.*, **1948**, *34*: 82-94.

SUGITA, NAOKI. Comparative studies on the growth of the cerebral cortex. II. On the increase in the thickness of the cerebral cortex during the postnatal growth of the brain - albino rat. *J. comp. Neurol.*, **1917**, *28*: 511-591.

SUGITA, NAOKI. Comparative studies on the growth of the cerebral cortex. V. Part I. On the area of the cortex and on the number of cells in a unit volume, measured on the frontal and sagittal sections of the albino rat brain, together with the changes in these characters according to the growth of the brain. Part II. On the area of the cortex and on the number of cells in a unit volume measured on the frontal and sagital sections of the brain of the Norway rat (Mus Norvegicus) compared with the corresponding data for the albino rat. *J. comp. Neurol.*, **1918**a, *29*: 61-96.

SUGITA, NAOKI. Comparative studies on the growth of the cerebral cortex. VI. Part I. On the increase in size and on developmental changes of some nerve cells in the cerebral cortex of the albino rat during the growth of the brain. Part II. On the increase in size of some nerve cells in the cerebral cortex of the Norway rat compared with corresponding changes in the albino rat. *J. comp. Neurol.*, **1918**b, *29*: 119-151.

SUITSU, M. Comparative studies on the growth of the corpus callosum. I. On the area of the corpus callosum measured on the section of the albino rat brain. *J. comp. Neurol.*, **1920**, *32*: 35-60.

SUTIN, J. and CAMPBELL, B. A model of cortical activity. *Nature*, **1955**, *175*: 338-339.

TANG, Y. On the development of different placing reactions in the albino rat. *Chin. J. Physiol.*, **1935**, *9*: 339-344.

TYLER, D. and VAN HARREVELD, A. The respiration of the developing brain. *Amer. J. Physiol.*, **1942**, *136*: 600-603.

VAN HARREVELD, A. Asphyxial depolarisation in the spinal cord. *Amer. J. Physiol.*, **1946**, *147*: 669-684.

VAN HARREVELD, A. and STAMM, J. S. Effect of pentobarbital and ether on the spreading cortical depression. *Amer. J. Physiol.*, **1953**a, *173*: 164-170.

VAN HARREVELD, A. and STAMM, J. S. Cerebral asphyxiation and spreading cortical depression. *Amer. J. Physiol.*, **1953**b, *173*: 171-175.

VAN HARREVELD, A. and STAMM, J. S. Relation between asphyxial damage to the cortex and the spreading depression. *Amer. J. Physiol.*, **1954**a, *178*: 117-122.

VAN HARREVELD, A. and STAMM, J. S. Consequences of cortical convulsive activity in rabbit. *J. Neurophysiol.*, **1954**b, *17*: 505-520.

WAELSCH, H., SPERRY, W. H. and STOYANOFF, V. A. The influence of growth and myelination on the deposition and metabolismus of lipids in the brain. *J. biol. chem.*, **1941**, *140*: 885-897.

WEILL, J. D. et MANDEL, P. Etude sur la consommation d'oxygène du cerveau à divers âges chez le rat blanc. *C. R. Soc. Biol.*, **1953**, *147*: 1818-1821.

Reference: BURES, J. The ontogenetic development of steady potential differences in the cerebral cortex in animals. *EEG Clin. Neurophysiol.*, **1957**, *9*: 121-130.

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THE RELATIONSHIP OF ALPHA AMPLITUDE TO THE LEVEL OF PALMAR CONDUCTANCE [1]

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A great number of articles, appearing in the physiological and psychological literature, have dealt with the problem of explaining amplitude variations of the alpha rhythm. The explanations have ranged from complex personality traits, through hereditary determinants, to physiological mechanisms. In the matter of experimental evidence, an often recurring finding has been the appearance of correlations between alpha amplitude and peripheral indicants of autonomic function such as heart rate, respiration rate, and GSR. These correlations are mostly negative (Darrow *et al.* 1946) (high autonomic activity being related to low alpha amplitude) and only moderate in size (values seldom exceeding — .50). As Obrist (1950, cited by Ellingson 1956) states, the assumption underlying this correlational approach has been that "... degree of arousal is directly proportional to GSR and inversely proportional to alpha amplitude" (p. 16). It is this assumption that we wish to bring under closer scrutiny in this paper.

As early as 1936, Jasper (1936) described the EEG characteristics that accompany changes in the "level of excitation". He pointed out that, as a S goes from a stage near sleep to one of moderate excitation, there is first an increase and then later a decrease in alpha amplitude. Darrow (1946, 1947) has also commented on this point and argued for positive correlations of autonomic activity and alpha amplitude during rest with negative correlations during stimulation. Finally, Lindsley (1952) has presented a table in which he attempts to relate EEG characteristics to a "behavioral continuum" of states of the organism. Here we can see plainly that, if we had some other physiological criterion of the "state of excitation" or level of arousal, we should expect to find an inverted-U relationship between this criterion measure and alpha amplitude.

Schlosberg (1954) has recently suggested that the level of palmar conductance [2] would be a suitable criterion measure. Conductance *level* should be differentiated from the GSR or galvanic skin *response*. The former refers to the slow, long-term changes (usually balanced out on the typical GSR apparatus) while the latter refers to the relatively rapid changes occasioned by discrete stimulation. GSR bears a relationship to conductance level analogous to that of a wave to a tide.

A study by Craig (1936) demonstrated that the level of palmar conductance was low in Ss who were resting quietly and still lower in Ss who fell asleep. Kleitman (1939) reports similar findings from the study of diurnal variations in conductance. Lindsley (1951) has summarized similar data on the relationship of conductance to level of arousal as follows: "Skin resistance increases under light anesthesia and during sleep, and it is high in newborn infants; in all these instances the level of diencephalic and forebrain excitation or activation is reduced, probably owing to decreased sensory influx" (p. 475).

It would seem, therefore, that the level of palmar conductance provides a suitable criterion measure in terms of which variations in alpha amplitude could be investigated. The

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[2] Conductance is the reciprocal of resistence.

present paper represents part of a larger study (Stennett 1956) in which relevant data, bearing on the hypothesis that an inverted-U relationship exists between alpha amplitude and conductance level, were obtained.

METHOD

Subjects

The Ss for this experiment were 31 men enrolled in various faculties and courses at McGill University. Their ages ranged from 17-23 years and they were paid for their services.

Procedure

Continuous recordings of several physiological variables including palmar conductance and EEG were taken from each S over a testing session which lasted from 3-4 hours. The testing period was broken up into four, basically different conditions designed to produce widely-varying states of arousal.

The first of these conditions was a 10-20 min. period during which the S was seated in a semi-reclining chair and merely requested to try to fall asleep.

During the next three conditions the S, still blindfolded, was required to complete 20 to 30, 2-min. trials of an auditory tracking test. This test required the S to track a systematically-varying point-of-no-sound or "auditory null point" by appropriate rotation of a controller knob. The test was arranged so that excellence of performance and the amount of sound heard by the S were inversely related. During these tracking trials the circumstances surrounding the S's performance were varied in an attempt to produce definite changes in level of arousal.

The first block of 10-20 trials was set aside as a "learning" condition. During this phase the S was given constant encouragement from the experimenter to try to better his best score and was offered small financial rewards (25 cents) each time he did so.

The next condition consisted of a block of four tracking trials given to the S under the guise of their being necessary for the experimenter to re-calibrate the recording equipment. It was explained to the S that, since the experimenter was busy with "calibration" procedures, scores could not be recorded.

A second block of four trials which constituted the next condition was presented to the S as a test of how well he could perform under "stress". The stress consisted of an opportunity for the S to win a bonus of from \$2.00-\$5.00 and avoid an electric shock (100-150 V.) each time he could equal or better his best score up to that point.

A final "resting" condition similar to that at the beginning of the experiment was presented to the S when all tracking trials had been completed. The line up of conditions and the corresponding level of arousal expected to result from them is shown in table I.

TABLE I

EXPERIMENTAL CONDITIONS AND THEIR PRESUMPTIVE AROUSAL VALUES

Conditions	*Subjects' Activity*	*Expected Arousal Values*
Initial Resting	Resting	Very low
Learning	Tracking — moderate incentive	Moderate
"Calibration"	Tracking — no incentive	Low
Stress	Tracking — high incentive	High
Final Resting	Resting	Very low

The order of presentation of calibration and stress conditions was alternated with successive Ss.

Apparatus and Technique

EEG. EEG was recorded on one channel of a custom-built, eight-channel, Edin EEG (the other seven channels were used to record other variables not considered here). Filters for this channel were set to pass 5-50 c/sec. From this primary recorder the signal was fed to a "band-pass integrator" (Davis 1956), which combined the response characteristics of two electronic resonator circuits to produce a flat-topped, band-pass characteristic between 8 and 13 c/sec. This was used to obtain selective sampling of the alpha component of the EEG.

The output of this "integrator", discharged automatically at 4-sec. intervals by an electronic synchrotimer, was recorded on one channel of a secondary, eight-channel ink-writer, the other channels of which were used to record other integrated data. All measurements were made from this integrator record in millimeters and transformed into microvolt values by reference to calibration standards.

Conductance. The circuit used for measuring d.c. skin resistance (from which conductance values were calculated) was a standard comparator bridge with sufficient voltage and series resistance to guarantee constancy of current (45 μA. d.c., ± 2 per cent) through the S over the range of resistances from 0 to 80 K Ω, with only slightly greater current changes for resistances up to 200 K Ω. A standard decade resistance box was used to balance the bridge and the circuit was arranged so that, when balanced, the decade resistance reading was equal to the S's resistance. A d.c. amplifier and recording galvanometer were used as a null-indicating device and changes in the S's resistance were measured as unbalance of this null reading (1000 ohms change in the S's resistance produced a 45 mV. bridge unbalance which, for impedance-matching purposes, was attenuated by a factor of 10 and thus appeared at the d.c. amplifier input as a 4.5 mV. signal). Calibration was arranged so that each 3 mm. of pen deflection represented 1000 ohms resistance change.

Measurement of resistance was made only to the nearest 333 ohms to ensure that the unit of measurement was always greater than any apparatus error. The resistance values were converted to micromhos (conductance units) by a reciprocal transformation and all subsequent calculations were done on these transformed values.

Lead placement. EEG was recorded from a single, bipolar, sponge-type electrode located along the mid-line such that one of the pair was located on the frontal area, the other over the parietal. This nonstandard placement was used firstly to minimize eye-movement artifacts and secondly as a compromise to provide sampling of both alpha and beta by using a single lead.

The electrodes for recording conductance were of the typical silver-silver chloride type and were approximately 1 sq. cm. in size. They were inserted into 1 inch cubes of cellulose sponge which were soaked in saline. These

TABLE II

RAW DATA FROM ONE SUBJECT ILLUSTRATING THE TABULATIONAL PROCEDURE USED TO TEST THE INVERTED-U HYPOTHESIS

Sections	*Rank-ordered conductance values (micromhos)*	*Corresponding alpha amplitude values (microvolts)*	*Conductance means*	*Alpha amplitude means*	*Redesignations of sections with reference to "optimal alpha"*
	I(a)	II(a)	I(b)	II(b)	
	54.0	11.0			
	56.7	12.7			
A	58.6	16.7	58.13	13.73	−3
	59.3	15.0			
	59.3	13.8			
	60.9	13.2			
	63.8	17.8			
	64.4	14.1			
B	65.1	21.7	65.30	18.30	−2
	65.4	16.3			
	66.5	20.0			
	66.6	19.9			
	68.3	22.4			
	68.4	17.4			
C	68.9	21.7	69.80	19.23	−1
	70.5	20.2			
	70.8	14.0			
	71.9	19.7			
	72.1	22.3			
	72.1	22.7			
D	73.1	18.6	73.70	20.65	0
	74.1	20.7			
	75.1	19.5			
	75.7	20.1			
	77.8	17.4			
	78.5	19.3			
E	79.1	15.7	79.92	17.45	+1
	79.6	17.9			
	79.8	17.9			
	84.7	16.5			

TABLE III

MEAN MICROMHO CONDUCTANCE VALUES FOR ALL SUBJECTS ARRANGED ACCORDING TO CATEGORIES

	Categories								
Subjects	*−4*	*−3*	*−2*	*−1*	*0*	*+1*	*+2*	*+3*	*+4*
1		13.97	14.31	15.20	15.66	16.54			
2		58.13	65.30	69.80	73.70	79.92			
3					12.97	25.38	28.55	29.70	33.75
4				40.53	51.48	56.32	58.63	61.85	
5				45.47	52.77	57.17	64.75	78.73	
6			55.51	62.29	69.41	73.60	76.62		
7				61.43	65.20	67.03	69.35	73.14	
8			43.29	50.79	56.56	58.29	60.35		
9				45.51	51.09	58.31	61.73	63.86	
10					20.04	28.30	34.33	41.54	43.77
11			126.00	135.00	145.20	157.90	176.08		
12			102.33	117.27	127.83	138.57	145.02		
13					87.77	95.18	101.47	108.30	117.69
14				47.46	51.10	53.77	60.73	67.95	
15				35.36	47.20	50.86	53.43	72.42	
16				79.60	90.09	97.25	105.73	111.20	
17				67.60	73.60	78.86	84.69	123.42	
18				38.47	55.51	87.19	111.46	143.55	
19					38.33	55.27	62.46	70.38	73.18
20	35.87	52.34	59.58	66.65	98.57				
21					86.10	101.76	106.87	112.76	130.26
22				80.81	94.07	96.43	98.38	102.65	
23		80.75	86.72	98.77	103.70	109.19			
24	72.05	91.50	99.37	103.35	110.06				
25		105.56	110.44	116.84	122.41	130.00			
26	45.48	65.57	74.67	77.80	83.33				
27					31.34	69.71	81.09	85.41	90.67
28				64.91	74.64	77.74	79.60	82.70	
29		31.16	65.64	100.06	108.64	115.91			
30				89.03	95.82	99.85	102.97	109.04	
31					64.67	92.10	105.47	119.37	128.07
Category Means		67.63		71.25	72.87	81.59	83.90	87.51	

sponge-covered electrodes were placed on the palm and dorsum of the S's left hand, covered with 2 in. square pieces of thin rubber (to prevent evaporation of the saline) and held in place by a lastonet band.

Measurement of the Records

Alpha amplitude values for all tracking trials were obtained by summating the amplitude of the 30 integrator waves occurring in each 2-min. period and then dividing this sum by 30 to give a mean. Values from the 1-min. samples during the resting conditions were obtained by summating the amplitude of the 15 integrator waves in each period and dividing by 15.

Measurements of palmar resistance were made at the beginning and end of each trial and every 15 sec. during the trial. This produced 9 measurements which, when converted to micromhos, were averaged to give one value for each trial. Similar average values

TABLE IV

MEAN MICROVOLT ALPHA-AMPLITUDE VALUES FOR ALL SUBJECTS ARRANGED ACCORDING TO CATEGORIES *

	Categories								
Subjects	*−4*	*−3*	*−2*	*−1*	*0*	*+1*	*+2*	*+3*	*+4*
1		4.46	4.63	4.68	5.19	5.02			
2		13.73	18.30	19.23	20.65	17.45			
3					13.86	12.87	11.39	10.87	10.78
4				16.13	18.28	16.60	15.36	14.52	
5				11.81	13.15	12.23	12.19	11.42	
6			11.03	14.11	18.46	17.74	16.35		
7				17.03	17.12	15.40	15.02	14.43	
8			10.98	8.93	11.97	11.57	10.52		
9				10.40	11.52	10.92	9.18	7.55	
10					10.73	9.43	9.51	9.58	9.49
11			18.81	20.77	21.47	20.50	18.78		
12			29.37	28.91	31.63	30.29	30.32		
13					23.71	22.42	23.56	22.04	22.49
14				15.92	22.97	21.59	21.42	22.48	
15				11.39	12.00	11.66	9.24	11.53	
16				27.20	30.04	29.29	27.86	26.88	
17				12.79	16.25	14.63	13.69	11.50	
18				15.77	23.96	23.38	17.90	21.43	
19					14.17	10.48	10.76	10.15	10.38
20	12.51	12.29	14.06	14.98	15.16				
21					6.99	5.75	5.97	6.63	5.88
22				6.76	7.42	6.65	7.26	7.06	
23		33.51	31.61	34.76	35.53	31.74			
24	17.12	15.68	25.26	24.38	25.93				
25		15.43	15.20	16.59	16.72	15.68			
26	7.98	8.83	8.84	9.48	9.77				
27					21.76	16.70	15.40	11.14	13.30
28				22.64	26.04	25.94	25.59	24.44	
29		6.32	8.96	17.85	23.18	23.02			
30				9.02	23.54	23.27	20.75	21.40	
31					27.69	24.24	23.32	24.24	21.63
Category Means		14.99		16.32	18.61	17.37	16.15	14.74	

* The values presented in this table are those which correspond to the mean conductance values of table III.

were obtained for the resting condition by measuring sections of the "conductance" record which corresponded in time to those measured for alpha amplitude.

RESULTS

Because none of the more conventional statistics were applicable to our data, we had to resort to a nonparametric test. The procedure (illustrated from the data of one S in table II) was as follows: for each S the average conductance values for each "trial" of the experimental session were rank-ordered in one column. Corresponding alpha-amplitude values were tabulated in a second column, and the data were then divided into 5

successive and equal sections. The means of the conductance and alpha-amplitude values in each of the 5 sections were calculated.

Since there was not a priori reason for assuming either that each S had values distributed over the entire arousal (conductance) continuum or that all Ss had values in exactly the same range of the continuum, we had to find some method of locating each S's position separately. We decided that the best method of accomplishing this was to find for each S the conductance value corresponding to his peak or optimal alpha amplitude. This was done by simply determining in which of the 5 sections the S showed the highest mean alpha (in the example of table II, section D). The appropriate conductance value then was simply the mean of that section which, for tabulational purposes, was redesignated as the O category. Sections in which the conductance means were successively *less* were then redesignated -1, -2, -3, and -4 respectively and sections in which the conductance means were successively *higher* were redesignated $+1$, $+2$, $+3$, $+4$.

With the data arranged in this way, we were in a position to reduce a test of the inverted-U hypothesis to the following terms: (*a*) alpha means in categories -2, -3, and -4 should be less than those in category -1; (*b*) alpha means in categories -3 and -4 should be less than those in category -2; (*c*) alpha means in category -4 should be less than those in category -3; similarly, (*d*) alpha means in categories $+2$, $+3$, and $+4$ should be less than those in category $+1$; (*e*) alpha means in categories $+3$ and $+4$ should be less than those in category $+2$; (*f*) alpha means in category $+4$ should be less than those in category $+3$. (Since zero category values were selected by inspection of the data, they could not legitimately enter into any statistical test.)

In table II we can see that for this S there were only three possible comparisons ($13.73 < 18.30$; $13.73 < 19.23$; $18.30 < 19.23$) and that all were in the direction required by hypothesis. It will be noted that this S had no values in categories -4, $+2$, $+3$, and $+4$. This is because our handling of the data allows for each S only 5 alpha amplitude values which may distribute themselves over any 5 successive categories of the 9 available.

Table III shows the conductance means for all Ss arranged according to categories. Table IV shows the corresponding alpha-amplitude means similarly arranged. From table IV, 119 comparisons of alpha-amplitude means were possible. Of these, 88 (74 per cent) were in the direction predicted by our hypothesis. Since by chance we would expect to have only 59.5 (50 per cent) of the comparisons occur as predicted, we could apply a χ^2 test of significance. The χ^2 obtained (27.30) is highly significant since, with one degree of freedom, a χ^2 of only 10.83 is required for significance at the .001 level of confidence.

In order to provide some graphical presentation of the significant group trend indicated by our statistical test the means of the columns (categories) of tables III and IV were calculated. However, since the -4, -3, and -2 categories were rather poorly represented, the data falling in them were grouped to give a single mean value. The data falling in categories $+3$ and $+4$ were treated similarly for the same reason. The resulting six pairs of alpha amplitude and conductance means were plotted in figure 1

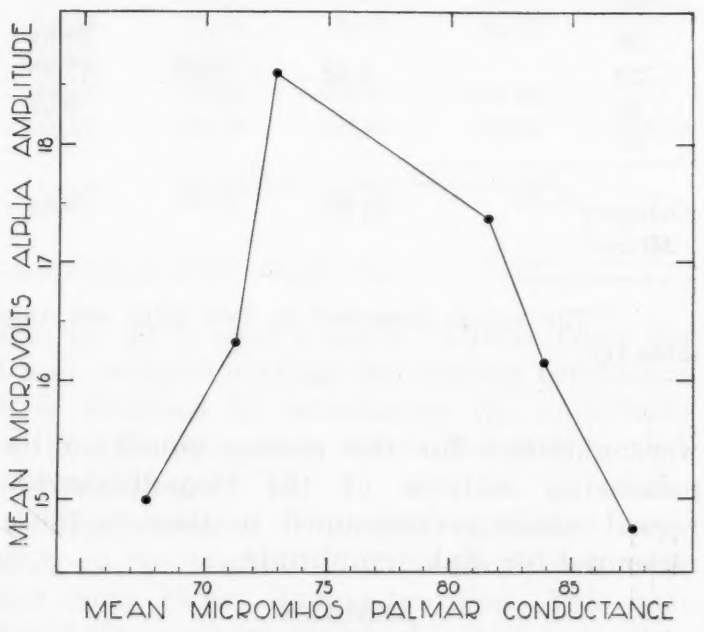

Fig. 1

The relationship of alpha amplitude to the level of palmar conductance.

which illustrates the relationship of alpha amplitude to the level of palmar conductance.

There are two points of caution to be noted in interpreting figure 1. Firstly, as may be noted by examination of tables III and IV, all Ss did not contribute to the determination of all points plotted.[1] Secondly, the curve should properly be considered as what one might expect to find in a single S *if* his alpha and conductance values were obtained over the *entire* range of the arousal continuum. That the curve does not describe the typical finding for each S in this experiment taken separately can be noted from table IV. For example, we can see that whereas Subject 6 had values distributed symmetrically about his peak alpha, Subject 26 had values only to the left of his peak and Subject 3 had values only to the right.

DISCUSSION

The results of this experiment offer fairly conclusive evidence that the relationship between alpha amplitude and the level of palmar conductance takes the form of an inverted-U. It should be noted, however, that figure 1 does not represent the precise shape of the relationship, since the shape depicted is partly a function of the way in which the data were handled for statistical purposes, and partly a function of the particular arousal states produced by the conditions of this experiment.

The fact that most reported correlations between alpha amplitude and other physiological variables are low and negative finds ready explanation in terms of this inverted-U relationship. Most of the Ss in these experiments (as in the present one) were, no doubt, in the region of the arousal continuum where a negative relationship obtains while a few were in the region where the relationship is positive. Thus, presenting the Ss with discrete stimulation would cause a reduction of alpha in most but "facilitation" in some such that the size of any correlation coefficient would be considerably attenuated — its sign being negative.

The implications of the results reported here are twofold. First, they serve as a reminder of an important methodological consideration in the study of EEG phenomena, viz., that the influence of the particular experimental effect studied be evaluated in terms of the position that the S occupies on the arousal continuum. Second, they point to the possible fruitfulness of a systematic study of the entire EEG spectrum with palmar conductance level as the reference axis. The results of such a study, especially if conducted with the aid of a frequency analyzer, would seem to provide data of significant methodological and theoretical importance.

[1] It might be inferred that the reason the mean alpha amplitude values are lower in the extreme categories was that those Ss contributing to these categories were low alpha "producers". In order to check this possibility, the Ss who contributed values in the extreme categories were compared statistically, with respect to maximum alpha produced (zero category value) during the experiment, with those who did not so contribute. Since the comparison showed that the two groups of Ss could be regarded as samples drawn from a common population, (with respect to maximal alpha production) the argument stated above has no basis.

SUMMARY

In a study of the relationship of alpha amplitude to the level of palmar conductance, 31 experimental Ss underwent several experimental conditions designed to produce substantial changes in level of arousal. Data from the continuous, selective recording of the alpha component of the EEG and palmar conductance gave highly significant statistical support to the hypothesis that an inverted-U relationship exists between these two variables.

The writer would like to acknowledge the aid and allocation of laboratory facilities by Dr. R. B. Malmo who supervised this research. The author is also indebted to Dr. J. F. Davis for his technical assistance and Mr. R. E. Quilter for his help in collecting the data.

REFERENCES

CRAIG, D. R. An investigation of basic skin resistance levels during sleep under differing conditions. Unpublished master's thesis, Indiana Univer., **1936**.

DARROW, C. W. Psychological and psychophysiological significance of the electroencephalogram. *Psychol. Rev.*, **1947**, *54*: 157-168.

DARROW, C. W., PATHMAN, J. H. and KRONENBERG, G. Level of autonomic activity and the electroencephalogram. *J. exp. Psychol.*, **1946**, *36*: 355-365.

DARROW, C. W., PATHMAN, J. H. and KRONENBERG, G. Autonomic indications of excitatory and homeostatic effects on the electroencephalogram. *J. Psychol.*, **1942**, *14*: 115-130.

DAVIS, J. F. Low frequency analyzers in electroencephalography. *Eleventh Ann. Meeting Instrum. Soc. Amer.*, N.Y.C., Sept. 1956, Paper No. 56-24-1 (to be published).

ELLINGSON, R. J. Brain waves and problems of psychology. *Psychol. Bull.*, **1956**, *53*: 1-34.

JASPER, H. H. Cortical excitatory state and synchronism in the control of bioelectric autonomous rhythms. *Cold Spr. Harb. Symp. Quant. Biol.*, **1936**, *4*: 320-338.

KLEITMAN, N. *Sleep and wakefulness.* Chicago, Univer. Chicago Press, **1939**.

LINDSLEY, D. B. Emotion. In S.S. Stevens (Ed.), *Handbook of Experimental Psychology.* New York, Wiley, **1951**, pp. 473-516.

LINDSLEY, D. B. Psychological phenomena and the electroencephalogram. *EEG Clin. Neurophysiol.*, **1952**, *4*: 443-456.

OBRIST, W. D. Skin resistance and electroencephalographic changes associated with learning. Unpublished doctor's dissertation, Northwestern Univer., **1950**.

SCHLOSBERG, H. Three dimensions of emotion. *Psychol. Rev.*, **1954**, *61*: 81-88.

STENNETT, R. G. The arousal continuum. Unpublished doctor's dissertation, McGill Univer., **1956**.

Reference: STENNETT, R. G. The relationship of alpha amplitude to the level of palmar conductance. *EEG Clin. Neurophysiol.*, **1957**, *9*: 131-138.

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AN ELECTROMYOGRAPHIC STUDY OF INDUCED AND SPONTANEOUS MUSCLE CRAMPS

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The cramps with which this paper deals we define as localized, involuntary, sustained and painful contractions of skeletal muscles. The onset is generally sudden, and there may be visible "knotting" of part or all of the affected muscle. Healthy persons experience cramps during vigorous exercise (e.g. "swimmers' cramps"), during sleep ("night cramps"), in pregnancy, and in a benign affection of the motor system, myokymia (Denny-Brown and Foley 1948; DeJong *et al.* 1951). A list of pathological conditions of which cramps may be a symptom includes low-sodium states and other electrolyte disturbances (Talbott 1935; Engel *et al.* 1949), uremia, B_1 avitaminosis (Jolliffe *et al.* 1939), ruptured intervertebral disc (Wolman 1949) and motor system degeneration (Brown 1951).

Despite a widespread belief that cramps occur in peripheral vascular disease, clinical studies have revealed no evidence of such a relationship (Gootnick 1943; Nicholson and Falk 1945; Thomas and Ajuriaguerra 1949; Naide 1950), except in the uncommon cases of spinal artery disease (Skinhøj 1954). To be mentioned in passing are other theories that cramps are caused by a virus (Verger and Delmas-Marsalet 1928), muscle herniation (Erben 1928), a "crampus disease" (Wilder 1940) and emotional disturbances (e.g. Holmes 1951).

It is still uncertain whether cramps have their origin in muscle or peripheral nerve (Denny-Brown 1953), or in the spinal cord (DeJong *et al.* 1951). Attempts to prove a spinal etiology, by means of spinal anesthesia, have given inconclusive and conflicting results (Grund 1927; DeJong *et al.* 1951). In previous electromyographic studies of cramps (Denning 1926; Denny-Brown and Pennybacker 1938; Denny-Brown and Foley 1948; Denny-Brown 1953) concentric needle electrodes have generally been used. These electrodes during cramps, as also during strong voluntary contractions, tend to record so many action potentials that finer interpretations are often difficult. On the other hand, electrodes with smaller recording area, though sampling electrical activity in less extensive regions of a muscle, are more apt to provide discrete records of single action potentials (Adrian and Bronk 1929; Lindsley 1935; Norris and Gasteiger 1955).

This paper describes the results of applying microelectrodes with recording areas about 10μ in diameter to a study of induced cramps in normal subjects and in certain patients who were known to suffer from spontaneous cramps. As stated in a preliminary report (Gasteiger, Norris and Chatfield 1955), it appears from these electromyograms that action potentials during both induced and spontaneous cramps may be due to activity of whole motor units. The effects of certain maneuvers and reflexes were also studied in order to determine what role the central nervous system may play in altering cramps of skeletal muscle.

METHODS AND MATERIALS

Electromyography. A detailed description of the microelectrodes used is given elsewhere (Norris and Gasteiger 1955). In brief, stainless steel wires were insulated with plastic, and the tips then drawn gently across a fine stone until small areas of about 100 μ^2 had

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been exposed. After sterilization these electrodes were inserted into muscle through hypodermic needles of suitable diameter, which served as cannulae. Paired recording electrodes were connected directly or via cathode follower circuits to Grass pre-amplifiers for push-pull amplification, and thence to a Dumont dual beam cathode ray oscilloscope. Action potentials were recorded on film moving at 50, 250 and 1,000 mm/sec. For comparison, a few recordings were made simultaneously with the microelectrodes and with concentric needle electrodes of several sizes. The finest concentric needle electrodes had two 39 μ silver center wires; the minimum recording area per wire being about 1134 μ^2 or about ten times the bared area of the microelectrodes. Occasionally, however, these concentric electrodes recorded with a selectivity equal to that of the microelectrodes. For general exploration or for special purposes some less accurate records were obtained by connecting the electrodes to an 8-channel Grass inkwriting electroencephalograph (muscle filters off) running at 60 mm/sec. Skin electrodes were also used in some cases.

Subjects. A preliminary study of the incidence of cramps was made on 121 college students, of whom 115 reported that they had experienced spontaneous cramps at least once. In addition, cramps were deliberately induced, as described under "observations", in *rectus femoris* and *gastrocnemius* muscles of 5 healthy young adult volunteers into whose muscles 2-6 electrodes had been inserted. Similar studies were carried out in 4 patients at the Clinical Center of the National Institutes of Health, Bethesda, Maryland.

Case 1 (N. I. H. 00-22-42), J. B., had multiple sclerosis and was developing a spastic, incomplete paraplegia with frequent muscle cramps.

Case 2 (N. I. H. 00-20-51), B. D., had disabling cramps and was developing spastic quadriplegia, which at operation was found to be caused by cervical arachnoiditis.

Case 3 (N. I. H. 00-18-10), W. M., had benign myokymia and frequent cramps.

Case 4 (N. I. H. 00-21-68), P. G., had acute anterior poliomyelitis with painful muscle cramps.

The action potentials observed during induced and spontaneous cramps were also compared with those recorded from muscles of 20 other patients with myotonia, muscular dystrophy or denervation. The results from study of this group have been reported in a separate publication (Norris and Chatfield 1955).

OBSERVATIONS

Incidence of cramps and their induction for experimental study. One obstacle to systemic study of cramps has been the unpredictability of their occurrence. Cramps are fairly prevalent, however, even in normal subjects. Careful questioning of 121 college students in physical training classes revealed that 115 had experienced spontaneous muscle cramps at least once. Of these 115, 18 (or 16 per cent) stated that they were awakened from sleep more often than twice per month by cramps, usually of the calf muscles. This confirms the high prevalence of "night cramps" found in healthy young people by other investigators (Wilder 1940; Nicholson and Falk 1945; Hall 1947).

A relation between cramps and muscle shortening has been noted by others, but has not previously been exploited for the systematic study of cramps (Denning 1926; Guillain *et al.* 1932; Gootnick 1943; Nicholson and Falk 1945; Page and Page 1953). One of us (F. N.) found that cramps could be induced in certain muscles by arranging the extremity so that the muscle under study was passively shortened, and then asking the subject to produce a maximum voluntary contraction. For example, to induce a cramp in the *biceps brachii,* the subject held his arm well flexed at both elbow and shoulder, and then made his greatest sustained *biceps* effort. Maximum *biceps* effort was continued until a cramp developed, but not longer than one minute. The subject used the right arm before, and the left arm after a brief period of general exercise, e.g. 20 min. in swimming classes or 30 min. of calisthenics. Induced cramps were reported by 18 per cent of the 115 subjects before exercise and by 26 per cent afterward. Of those reporting cramps, about one-third induced cramps both before and after exercise.

Induced cramps, when they appeared, began within 10 to 60 sec. after maximal contraction was started. The onset was generally gradual with rapid growth in intensity or, in some instances, they were sudden and intense from the start. Fully developed induced cramps were localized, involuntary once initiated, sustained, and painful. Visible knotting of the biceps or localized hardness on palpation were found in many instances. The traction induced cramps with the same characteristic in the *rectus femoris* and *gastrocnemius* muscles. Electromyography of these muscles was technically simpler and they were therefore selected for detailed study.

To induce cramps in the *rectus femoris* the subject sat with the leg supported so that the knee was fully extended, thus shortening the *rectus femoris* passively. Then the subject was asked to contract the extensors of the

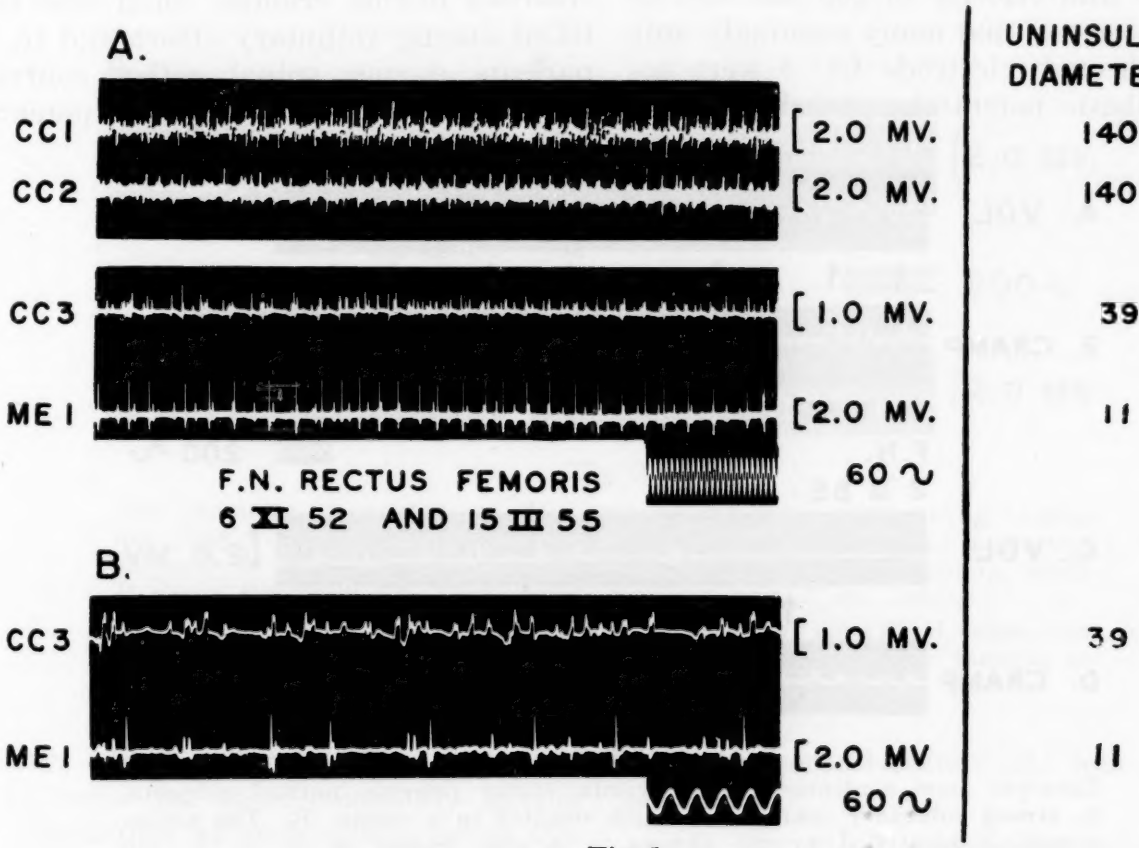

Fig. 1

Excerpts from activity during strong voluntary contraction. CC1 and CC2 were obtained from concentric needle electrodes with copper center wires 140μ in diameter. CC3 shows the greater selectivity and more discrete record obtained by using a concentric needle electrode with a silver center wire 39μ in diameter. Still greater selectivity resulted from using microelectrodes (ME 1) with uninsulated areas about 11μ in diameter.
However, what appears to be adequate selectivity in the CC3 record of A (film speed 50 mm/sec.) is found to be much less discrete upon recording the same activity at 250 mm/sec. in B and contrasting it to the simultaneous microelectrode recording.

subjects complained of the painfulness of the induced cramp. They mentioned its involuntary nature and its similarity to spontaneous cramps previously experienced.

Initially, electromyograms were recorded from the *biceps brachii* during such induced cramps but limited space made it difficult to insert and fix multiple electrodes. It was then found that the maneuvers of prior passive shortening coupled with maximal contraction maximally. To induce cramps in the *gastrocnemius* the subject reclined prone, with the knee partially extended and the ankle fully extended to shorten the *gastrocnemius* maximally. These maneuvers induced cramps not only in a number of apparently normal subjects but also in patients with histories of frequent spontaneous cramps.

Action potentials recorded during cramp. Figure 1 illustrates the greater selectivity of

electrodes of small recording area, a recording characteristic essential for a study of this kind. During strong voluntary contractions of the *rectus femoris* muscle, recordings obtained through conventional concentric electrodes (CC1, 2 and 3), diameter 140 and 39 μ, are compared with recordings through microelectrodes (ME 1), diameter 11 μ. The greater selectivity of the electrodes with smaller recording diameters seems clear. Increasing the film velocity to 250 mm/sec. as in figure 1B reveals that many seemingly unit discharges through electrode CC 3 were actually polyphasic potentials, probably resulting from summation of activity of two or more units.

Selectivity of this order has, however, certain consequences. Owing to their limited recording field, microelectrodes occasionally failed to record electrical activity in weak voluntary contractions. This was more evident in cramps where the discharges are often localized to small portions of a muscle and may escape a microelectrode located even a small distance away. Hence, interpretation of records must take into account the selectivity of microelectrodes, the smaller expanse of muscle examined by them, and the frequent local nature of cramps.

Action potentials recorded during severe cramps are illustrated in figures 2 (B and D), 3 (A, B and D), and 4 (A and B). The potentials in any given series (e. g. in B and D of fig. 2) were nearly uniform, with no greater variation in amplitude and duration than is commonly recorded in voluntary contractions (see Seyffarth 1940; Norris and Gasteiger 1955).

With any one electrode position, action potentials, apparently identical with those recorded during cramps, could also be identified during voluntary effort and in spastic patients during spinal reflex contractions. For example, the same action potential recorded during a strong contraction (fig. 2A, indicated by the arrows) appeared during a cramp (fig. 2B). Another example is given in figure 2, C and D, recorded in this instance from concentric needle electrodes. The amplitude and duration of the action potentials were comparable to those of normal motor units and were clearly different from those of myotonic and denervated (fibrillating) muscle, records of which we have published elsewhere (see Norris and Chatfield 1955). There were no apparent differences between the discharges recorded in induced cramp and those observed in spontaneous cramps.

A given unit could discharge very rapidly

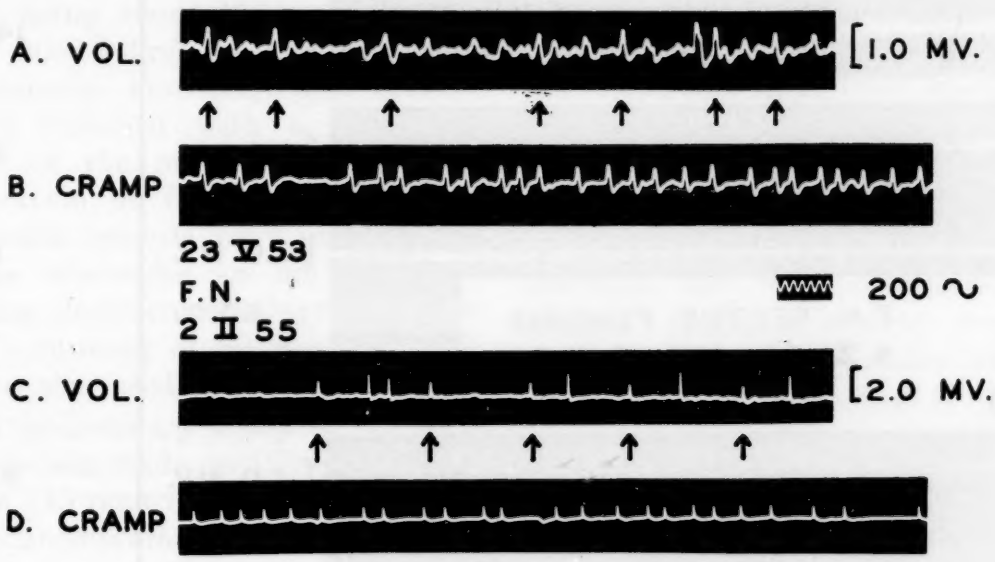

Fig. 2

Excerpts from continuous film records, *rectus femoris,* normal subjects. A, strong voluntary contraction which resulted in a cramp, B. The action potentials identified by the arrows in A also appear in B. C, D, the same, using a fine concentric needle electrode.

in a cramp, even faster than in voluntary effort (compare the activity in fig. 2A and B, 2C and D). While such discharge rates may be high for the units in question, they cannot be regarded as abnormal, when compared to other units which discharge even faster in voluntary contractions. As the pain of cramp faded away the discharge rate decreased.

Temporary synchrony of discharges of different motor units was occasionally found in voluntary contractions and after-discharges (see Norris and Gasteiger 1955), but they tended to occur far more commonly during cramps. Examples of such synchronous discharges are given in figure 3. Parts A and B are excerpts of activity recorded by two pairs of microelectrodes during a cramp, B being seven seconds after A. It should be noted that there is a clear contrast between the asynchrony of the activity between the two channels in A and the synchronized discharge of different units in B. Parts C and D of figure 3, recorded from the same electrode site, illustrate an apparently different electromyographic manifestation of synchronized activity. The large atypical discharges recorded during a cramp (D) were not present even in maximum voluntary effort (C), either before or after the cramp. Hence they were very likely caused by synchronous activity of different units, the action potentials having summated.

During cramps, the activity of a single unit did not appear to be systematically related to the pain experienced. The activity of the same unit recorded from the same electrode placement during two cramps is shown in figure 4; its activity was nearly identical in both cramps, as will be seen from comparison of A and B. Yet the first cramp (A) caused the patient, B. D., (case 2), to double up in agony and become speechless, with drops of perspiration appearing on his face, while the second cramp (B) was but slightly painful.

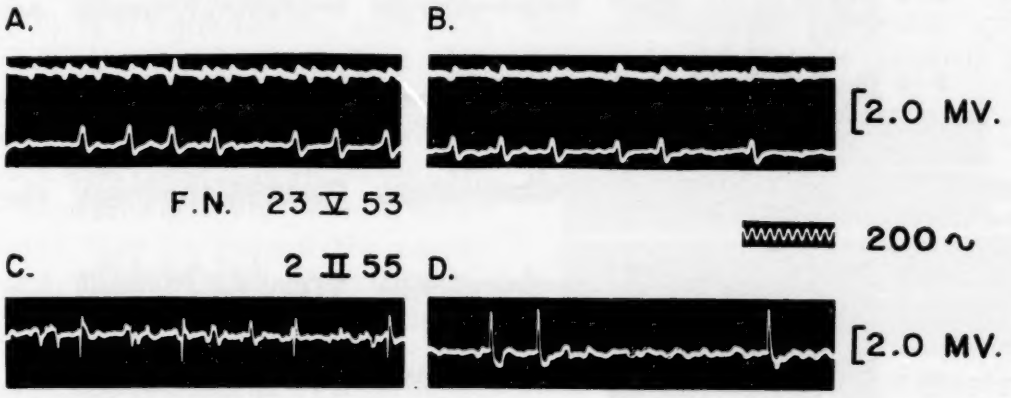

Fig. 3

Two examples of synchronous discharge of different units during cramps are illustrated from recordings of *rectus femoris* activity of a normal subject. A shows asynchronous firing of two units during cramp, while B shows the same two units firing synchronously 7 sec. later.

The large, broad waves recorded during another cramp, D, were not present during maximum voluntary effort, C, and hence are thought to reflect synchronous activity of 2 or more units.

On the other hand, the *total* electrical activity did reflect the degree of pain, as shown in figure 5 (this figure is treated in more detail below). Thus, the degree of pain would seem to be an indicator of the number of active units.

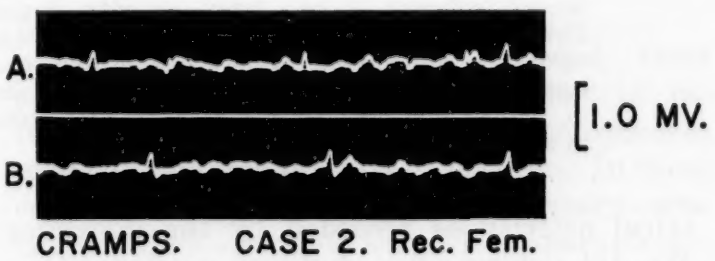

Fig. 4

Excerpts of activity by the same unit recorded during two cramps in *rectus femoris* of patient B. D. (case 2). The first cramp (A) was very severe, the second cramp (B) was only slightly painful.

Alteration of cramp activity. Various maneuvers were tried during cramps, as described below, and the effects were estimated in terms of the changes in pain as reported by the subject, and changes in the total electrical activity as recorded by the inkwriter. We did not consider slight or gradual variations significant, because cramps, though often well-localized, may shift to involve first one part, and then another of the same muscle; and in addition they tend to fade away over a period of seconds or minutes unless very severe.

One type of experiment in a normal subject is illustrated in figure 5. Five microelectrodes had been inserted into the right *rectus femoris* and connected in various combinations to the top seven inkwriter channels. Two skin electrodes over the left *quadriceps* muscles were connected to the bottom inkwriter channel. The first column of records shows the strong voluntary contraction in

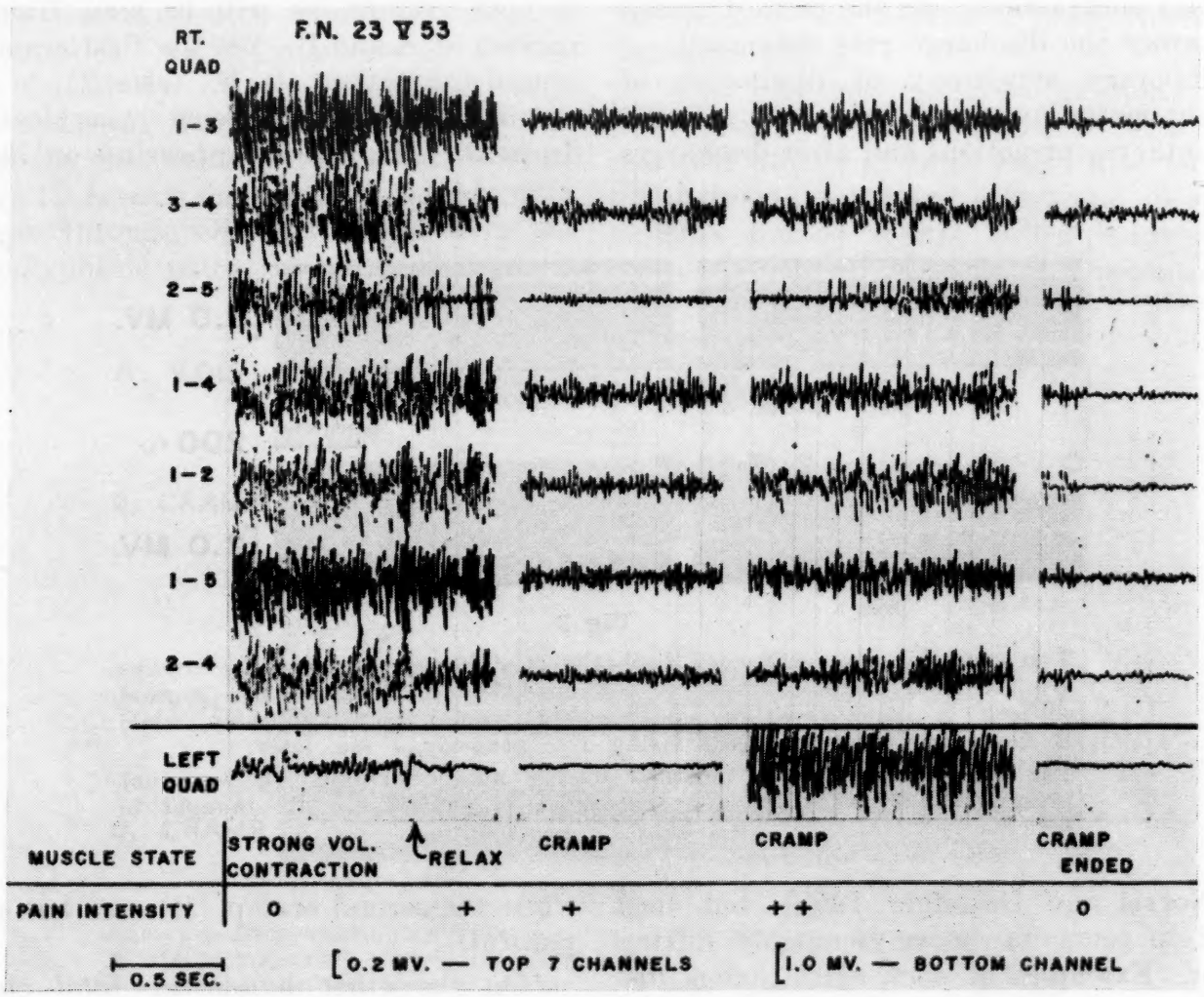

Fig. 5

Excerpts from continuous inkwriter records to show alteration of a cramp by contraction of the contralateral homologue during the cramp. Various pairs of 5 microelectrodes in the right *rectus femoris* were connected to the upper 7 channels; the lowest channel recorded activity picked up by skin electrodes over the left *quadriceps*.
First column: strong voluntary contraction of the right *rectus femoris*, with attempted relaxation (indicated by arrow) as the subject felt the muscle cramping.
Second column: 4 sec. later, activity during cramp; note subjective evaluation of pain.
Third column: about 5 sec. later, increase of activity in the cramped muscle during voluntary contraction of left homologous muscle, with subjective increase of pain.
Last column: continuing activity about 1 sec. after cramp had disappeared. Note variation in the amount of activity recorded on different channels during the cramp as contrasted to voluntary contraction.

right *rectus* which resulted in a cramp (note the involuntary activity recorded from the left side during the contraction on the right). The subject attempted to relax (indicated by the arrow), and all the remaining records show involuntary activity on the right side. When he made maximum voluntary effort on the left during the cramp on the right (third column in fig. 5), the cramp pain increased (from + to ++) and the records showed more activity in the cramped muscle. We interpret the changes to be an increase in the cramp activity in that both tension and pain increased. When the subject stopped this contraction on the left, the cramp on the right promptly became less painful and the recorded activity decreased.[1] The last column shows activity continuing a full second after the subject stated that he judged the cramp to have ceased entirely. The relationship between pain and total activity, mentioned above, should be noted. This experiment was repeated 6 times with similar results and once with no apparent change in the cramp.

Contraction of ipsilateral antagonists caused the cramps in the normal subjects to become less painful, with less electrical activity being recorded, even when care was taken to prevent stretching the cramped muscle. We observed this effect on 5 occasions, no change in the cramps being detected in two other instances. The effect on cramps in these experiments was presumably by means of reflex inhibition during reciprocal innervation.

The possibility arising from the studies on normal subjects that reflexes could affect cramps was supported by similar studies in the two spastic patients. B. D. (case 2) had found that he could bring on cramps in the left *quadriceps* muscles by stroking or pinching perineal skin; the skin sensation itself did not feel abnormal to him. Under electromyographic observation, there was an obvious relation, which the patient had also noted, between the duration and intensity of the skin stimulation and the resulting cramps.

[1] The effect in these experiments might be explained as increased motor activity due to increasing stimuli from higher centers and to heightened activity resulting from Phillipson's crossed extensor reflex.

The influence of shortening, in predisposing to cramps, is mentioned above, while stretching cramped muscles usually resulted in relief. However, we did observe one cramp in J. B. (case 1), which was clearly made worse by even the slightest stretching, and which was relieved by shortening. This was only the fourth such instance of the reversal of the effects of shortening and lengthening in the personal observation of about 3,000 cramps by one of us (F. N.)

Role of voluntary motor system. In the two paretic patients, motor units apparently not under voluntary control became active

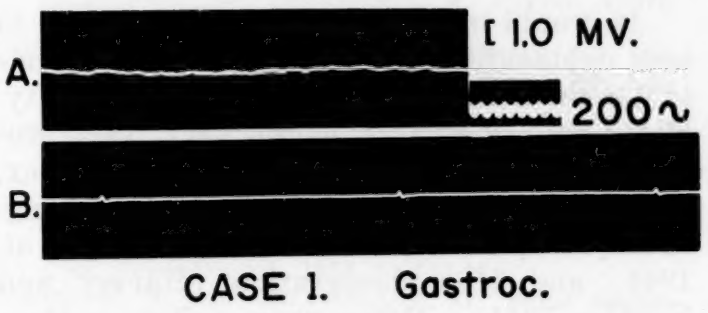

Fig. 6

Excerpts from continuous record of repeated voluntary contractions, cramps, and ankle jerks, made from the same electrode position in *gastrocnemius* of J. B. (case 1). A, typical record obtained during maximum voluntary effort, showing absence of voluntary control over the motor units in the range of the microelectrodes. B, record made during a cramp showing activity of a motor unit not under voluntary control, though excitable by ankle jerks.

during cramps. Figure 6A illustrates maximum voluntary effort as recorded from microelectrodes within the *gastrocnemius* of J. B. (case 1); it is apparent that there was no voluntary control over the motor units in the range of either microelectrode. Nevertheless, several units were excited during ankle jerks, and one of these was active during a mild cramp (fig. 6 B).

Moreover, the activity recorded from cramped muscles differed from that in voluntary efforts and in subconscious movements made during minor shifts of position. In these conscious and subconscious voluntary contractions, all channels showed comparable activity (e. g., the first column of records in fig. 5), while in cramps it was common to find virtual electrical silence on some channels (e. g., 2-5 in fig. 5) and intense activity on others (e.g., 1-3 in fig. 5). It seems, there-

fore, that the motor activity in cramps could originate independently of the voluntary motor system.

DISCUSSION

The muscle action potentials during cramps were so clearly different from those recorded during spontaneous presumably myogenic activity (e.g. myotonia, fibrillation) as to leave little doubt that cramp motor activity was due to excitation of most, if not all, the muscle fibers in a given motor unit. Moreover, these action potentials were often identical with known motor unit action potentials observed in voluntary contractions.

It would then seem most reasonable to seek explanation of cramp activity in terms of mechanisms producing motor unit activity. Motor unit discharge might have been produced peripherally by a motor axon reflex, which may be the genesis of fasciculation, e.g. in amyotrophic lateral sclerosis (Forster *et al.* 1946) and after denervation (Harvey and Kuffler 1944). Motor axon reflex, a theoretical concept at present, may be defined as a discharge of the whole motor unit resulting from firing of a terminal axon of the motor unit. Presumably this terminal axon would be in an abnormal hyperexcitable state. However, this mechanism would not account for the synchronous excitation of different motor units. It seems much more probable that the activity during cramps was caused by spinal, rather than peripheral, excitation of motor units, a likelihood which is supported by the effects of reflexes on cramps.

The motor activity in cramps might represent discharge in response to afferent stimuli — either abnormal or painful sensory impulses, or normal sensory impulses reaching hyperexcitable central reflex mechanisms. The cramps associated with spinal cord injury suggest that such a cramp producing focus of hyperexcitability can exist within the spinal cord. The high prevalence of cramps in healthy young adults suggests that the mechanism producing cramps is physiological, the unusual occurrence of cramps in certain diseases being due to exaggeration of normal function (Thomas and Ajuriaguerra 1949).

In that muscle pain differs in several respects from other types of pain, it is interesting to speculate as to what causes the pain of cramps. Cramp pain may not be relieved by morphine in large doses (Talbott 1935). It seems to result from more massive stimulation than is needed to produce cutaneous pain. Muscle biopsy and injection of solutions may be extremely painful whereas we have observed, as have others, that insertion and movement of electrodes within the muscle is not painful. Motor unit activity is not known to produce afferent impulses which are perceived as painful; however, in our study the pain in cramps seemed to be proportional to the total number of active units. Another important consideration is that the pain from cramps may be perceived in part from impulses conducted in dorsal column pathways, since spinothalamic tractotomy may relieve all pain but that of cramps (White 1954). This is also suggested in that the pain from involuntary post-ischemic contractions seems to be perceived in part via the dorsal columns (Merrington and Nathan 1949).

It appears that relief of cramp by lengthening the affected muscle was formely common knowledge: " . . . the muscles in general were afflicted also; so much that the patient would at times leap out of bed, and try to ease the pain by stretching his body in every direction". (Sydenham 1669).

Though relatively few modern physicians have noted this effect of stretching, it is well known among athletes (Karpovich 1953). By this simple procedure one can relieve cramps in most cases, presumably through the mechanism of autogenetic inhibition which Granit (1950) has described.

SUMMARY

1. "Night cramps" occurred in 16 per cent of 115 healthy young adults, confirming the findings of previous investigators.

2. Cramps were induced for laboratory study by maximum voluntary effort while the muscle was in a shortened position. Stretching of the affected muscles was an effective way of abolishing most cramps.

3. The muscle action potentials recorded during cramps were found to reflect motor unit activity.

4. Reflexes and other maneuvers altered and even initiated cramps in both normal

controls and neurological patients, supporting the likelihood that the motor activity in cramps was originating in the central nervous system.

REFERENCES

ADRIAN, E. D. and BRONK, D. W. The discharge of impulses in motor nerve fibers. Part II. The frequency of discharge in reflex and voluntary contractions. *J. Physiol.*, **1929**, *67*: 119-151.

BROWN, M. R. "Wetherbee Ail". The inheritance of progressive muscular atrophy as a dominant trait in two New England families. *New Engl. J. Med.*, **1951**, *245*: 645-647.

DEJONG, H. H., MATZNER, I. A. and UNGER, A. A. Clinical and physiological studies in a case of myokymia. *Arch. Neurol. Psychiat.*, Chicago, **1951**, *65*: 181-188.

DENNING, H. Uber den muskelcrampus. *Dtsch. Z. Nervenheilk.*, **1926**, *93*: 96-104.

DENNY-BROWN, D. Clinical problems in neuromuscular physiology. *Amer. J. Med.*, **1953**, *15*: 368-390.

DENNY-BROWN, D. and FOLEY, J. M. Myokymia and the benign fasciculation of muscular cramps. *Trans. Ass. Amer. Phys.*, **1948**, *61*: 88-96.

DENNY-BROWN, D. and PENNYBACKER, J. B. Fibrillation and fasciculation in voluntary muscle. *Brain*, **1938**, *61*: 311-334.

ENGEL, F. L., MARTIN, S. P. and TAYLOR, H. On the relation of potassium to the neurological manifestations of hypocalcemic tetany. *Bull. Johns Hopk. Hosp.*, **1949**, *84*: 285-301.

ERBEN, S. Ueber den Crampus und seine Bekämpfung. *Wien. klin. Wschr.*, **1928**, *41*: 1499-1501.

FORSTER, F. M., BORKOWSKI, W. J. and ALPERS, B. J. Effects of denervation on fasciculations in human muscle. Relation of fibrillations to fasciculations. *Arch. Neurol. Psychiat.*, Chicago, **1946**, *56*: 276-283.

GASTEIGER, E. L., NORRIS, F. H. and CHATFIELD, P. O. Electrical discharge from induced cramps. *Amer. J. Physiol.*, **1955**, *183*: 619.

GOOTNICK, A. Night cramps and quinine. *Arch. Intern. Med.*, **1943**, *71*: 555-562.

GRANIT, R. Autogenetic inhibition. *EEG Clin. Neurophysiol.*, **1950**, *2*: 417-424.

GRUND, G. Der lokale muskelcrampus als tonusphänomen. *Dtsch. Z. Nervenheilk.*, **1927**, *97*: 1-9.

GUILLAIN, G., ALAJOUANINE, T. et GARCIN, R. Crampes myoclonies et paralysie périphérique du sciatique poplité externe évoluant depuis six ans chez un parkinsonian postencéphalitique. *Rev. neurol.*, Paris, **1932**, *1*: 127-138.

HALL, A. J. Cramps and salt balance in ordinary life. *Lancet*, **1947**, *2*: 231-233.

HARVEY, A. M. and KUFFLER, S. W. Synchronization of spontaneous activity in denervated human muscle. *Arch. Neurol. Psychiat.*, Chicago, **1944**, *52*: 495-497.

HOLMES, T. H. Muscle spasms, professional cramp and backache. In Cecil, R. L. and Loeb, R. F., *A Textbook of Medicine*, Saunders, Philadelphia, **1951**, 8th ed., pp. 1443-1447.

JOLLIFFE, N., GOODHART, R., GENNIS, J. and CLINE, J. K. The experimental production of vitamin B_1 deficiency in normal subjects. *Amer. J. med. Sci.*, **1939**, *198*: 198-211.

KARPOVICH, P. V. *Physiology of Muscular Activity*, W. B. Saunders, Philadelphia, 4th ed., **1953**, pp. 25-27.

LINDSLEY, D. B. Electrical activity of human motor units during voluntary contraction. *Amer. J. Physiol.*, **1935**, *114*: 90-99.

MERRINGTON, W. R. and NATHAN, P. W. A study of postischaemic paresthesiae. *J. Neurol. Neurosurg. Psychiat.*, **1949**, *12*: 1-18.

NAIDE, M. Diphenhydramine (Benadryl) for nocturnal leg cramps. *J. Amer. Med. Ass.*, **1950**, *142*: 1140.

NICHOLSON, J. H. and FALK, A. Night cramps in young men. *New Eng. J. Med.*, **1945**, *233*: 556-559.

NORRIS, F. H. and GASTEIGER, E. L. Action potentials of single motor units in normal muscle. *EEG Clin. Neurophysiol.*, **1955**, *7*: 115-126.

NORRIS, F. H. and CHATFIELD, P. O. Some electrophysiological aspects of muscular dystrophy. *EEG. Clin. Neurophysiol.*, **1955**, *7*: 391-397.

PAGE, E. W. and PAGE, E. P. Leg cramps in pregnancy. *Obs. Gyn.*, **1953**, *1*: 93-100.

SEYFFARTH, H. The behaviour of motor-units in voluntary contraction. *Skr. norske VidenskAkad.*, **1940**, (no. 4) 1-63.

SKINHØJ, E. Arteriosclerosis of the spinal cord. *Acta Psychiat. Kbh.*, **1954**, *29*: 139-144.

SYDENHAM, T. Epistolae Responsoriae, I, 7, 1669, in Latham, R. G. (ed.) *The Works of Thomas Sydenham, M.D.*, vol. II, Sydenham Soc., London, **1848**.

TALBOTT, J. H. Heat cramps. *Medicine*, Baltimore, **1935**, *14*: 323-376.

THOMAS, A. and AJURIAGUERRA, J. de. Les états de grande hypertonie, *Etude Sémiologique du Tonus Musculaire*, Flammarion, Paris, **1949**.

VERGER, H. and DELMAS-MARSALET, P. Les myalgies rhumatismales. *Ann. Méd.*, **1928**, *23*: 301-318.

WHITE, J. C. Conduction of pain in man. *Arch. Neurol. Psychiat.*, Chicago, **1954**, *71*: 1-23.

WILDER, J. Crampus disease and localized muscular cramps. *Med. Rec.*, N. Y., **1940**, *152*: 442-446.

WOLMAN, L. Cramp in cases of prolapsed intervertebral disc. *J. Neurol. Neurosurg. Psychiat.*, **1949**, *12*: 251-257.

Reference: NORRIS, F. H., JR., GASTEIGER, E. L. and CHATFIELD, P. O. An electromyographic study of induced and spontaneous muscle cramps. *EEG Clin. Neurophysiol.*, **1957**, *9*: 139-147.

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ANNOUNCEMENT

SEVENTH INTERNATIONAL CANCER CONGRESS

London, England

July, 1958

Sponsored by

The International Union Against Cancer

The Seventh International Cancer Congress will be held in London, England, July 6-12, 1958 under the Presidency of Sir Stanford Cade. Congress headquarters will be The Royal Festival Hall.

There will be two main sessions of the Congress:

A. Experimental
B. Clinical and Cancer Control

Special emphasis will be placed on Hormones and Cancer, Chemotherapy, Carcinogenesis and Cancer of the Lung.

Proferred papers will only be considered if submitted with an accompanying abstract (not over 200 words) before October 1957 and if dealing with new and unpublished work.

The registration fee for the Congress will be £ 10 (ten pounds) or $30 (thirty dollars) and the latest date for registration without late fee will be *January 1, 1958.*

Registration forms and a preliminary program will be available early in 1957 on application to

The Secretary General
Seventh International Cancer Congress
45 Lincoln's Inn Fields
London, W. C. 2, England

J. H. MAISIN, *President*
Union Internationale Contre Le Cancer
Voer des Capucins, 61
Louvain, Belgium

HAROLD DORN, *Secretary General*
Union Internationale Contre Le Cancer
National Institute of Health
Bethesda 14, Maryland, U.S.A.

CLINICAL AND LABORATORY NOTES

Editor for Western Hemisphere and Far East, R. S. SCHWAB, M.D., Boston, U.S.A.
Editor for Europe and Middle East, F. BUCHTHAL, M.D., Copenhagen, Denmark

FAILURE OF A SINGLE LARGE DOSE OF ISONICOTINIC HYDRAZIDE AS AN ELECTROENCEPHALOGRAPHIC ACTIVATING PROCEDURE

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National Veterans Epilepsy Center, Veterans Administration Hospital, Boston 30, Mass.

(Received for publication: September 10, 1956)

Since no ideal ''activating'' procedure has been found, there is justification and hope in trying new techniques. This note is to report the failure of such a technique at least for the specific methods employed.

Convulsions have been reported in patients receiving isonicotinic hydrazide (INH) for the treatment of tuberculosis. This drug may aggravate an epilepsy (Fetterhoff *et al.* 1952; Vysniouskas and Brueckner 1954). Reilly (1952) induced seizures in patients by giving very large doses of INH plus photic stimulation. Related hydrazide compounds are recognized analeptics (Kopeloff *et al.* 1956; Pfeiffer *et al.* 1956; Stevens *et al.* 1952). Hence, it was hoped that a large single dose of INH which markedly exceed the usual 300-400 mg/day therapeutic dose might produce changes in the EEG of epileptics but not in non-epileptic patients.

RESULTS

Nineteen patients from the neurological service who had EEGs during the preceding week were given 10 to 20 mg/kilo body weight of Nydrazid[1] in a single intramuscular injection; serial electroencephalograms were then obtained over a period of 4 to 8 hours. Eleven of these patients had convulsive disorders, 1 had alcohol induced seizures, and 18 had intracranial pathology. Electroencephalograms consisted of bipolar, 10 electrode placement runs obtained while the patient was at rest but awake; 3 min. of hyperventilation was also included.

There were no significant changes in the EEGs except in 3 patients. In one case (patient S.M.) some spiky activity seen in the pre-INH EEG was not seen during any of the post-INH records; this patient had had a cerebral thrombosis without any convulsive disorder and his EEG was abnormal. In a second patient (J.J.T.) there was a greater ''build-up'' with hyperventilation in the 45 min. post-INH record than in any of his other EEGs; this patient had tension headaches, no evidence of neurological disease, and a normal EEG. The third patient (E. J.) had a convulsive disorder and an abnormal electroencephalogram; there may have been slightly more spikiness in the one hour post-INH record than in either the pre-INH record or in any of the other serial EEGs. There was no evidence of exaggeration of any existing focal EEG abnormalities.

One patient became nauseated several hours after the INH was given; whether this was due to the drug or not was not clear. Although alteration of deep muscle reflexes was not specifically tested for, no other untoward clinical side-effects were noted.

This lack of EEG alteration after administration of INH is at least in part in accord with the findings of Addington, Winfield, and Phillips (1954) and MacKinnon (1954).

SUMMARY AND CONCLUSIONS

Isonicotinic hydrazide given in large single IM doses ranging from 10-20 mg/kilo body weight caused no constant and probably no significant change in the electroencephalograms of neurological patients with or without a convulsive disorder. Hence, this technique appears to be unsuccessful as an ''activating'' procedure.

REFERENCES

ADDINGTON, M. C., WINIFIELD, D. L. and PHILLIPS, S. Effect of isoniazid upon the emotions and the electroencephalograms of tuberculous patients. *Amer. Rev. Tubercul.*, **1954**, *70*: 476-482.

FETTERHOFF, K. I., HOLMES, C. Y. and MARTIN, G. E. Hazards of isoniazid therapy in epileptics. *Amer. Rev. Tubercul.*, **1952**, *66*: 501.

KOPELOFF, L. M., CHUSID, J. G. and KOPELOFF, N. Convulsant effects of semicarbazide in epileptic monkeys. *Proc. Soc. Exper. Biol.*, **1956**, *92*: 132-134.

MACKINNON, I. H. in personal communication to: PLEASURE, H., Psychiatric and Neurological Side Effects of Isoniazide and Iproniazid. *Arch. Neurol. Psychiat.*, Chicago, **1954**, *72*: 313-320.

1 Nydrazid was supplied to us through the courtesy of M. H. Lund, M.D. of the Squibb Institute for Medical Research.

PFEIFFER, C. C., JENNY, E. H. and MARSHALL, W. H. Experimental seizures in man and animals with acute pyridoxine deficiency produced by hydrazides. *EEG Clin. Neurophysiol.*, **1956**, *8*: 307-315.

REILLY, R. H. Convulsant effects of isoniazide. *J.A.M.A.*, **1953**, *152*: 1317-1321.

STEPHENS, R. R. Grand mal convulsive seizures in patients receiving semicarbazide. *J. Pharmacol. Exp. Therap.*, **1952**, *106*: 418-419.

VYSNIOUSKAS, C. and BRUECKNER, H. H. Severe reactions of the central nervous system following isoniazid treatment. *Amer. Rev. Tubercul.*, **1954**, *69*: 759-765.

Reference: FRIEDLANDER, W. J. Failure of a single large dose of isonicotinic hydrazide as an electroencephalographic activating proceduce. *EEG Clin. Neurophysiol.*, **1957**, *9*: 149-150.

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TECHNICAL NOTES

Editor for Western Hemisphere and Far East, J. KNOTT, Iowa City, Iowa, U.S.A.
Editor for Europe and Middle East, H. SHIPTON, Bristol, England

APPARATUS FOR CHRONIC STIMULATION OF THE BRAIN OF THE RAT BY RADIOFREQUENCY TRANSMISSION

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Endocrinology Branch, National Cancer Institute and Laboratory Aids Branch, Instrument Section, National Institutes of Health, Bethesda, Md.

(Received for publication: July 9, 1956)

Various techniques have been devised in the past for stimulation of the brain. The majority of these have utilized direct leads passing from the impulse generator to intracranial electrodes which were firmly fixed to the skull. The major disadvantage to this type of apparatus is that the animals are not completely free to perform their normal activities during the time they are being stimulated.

Methods of remote stimulation have been designed previously. Harris (1948) utilized a subcutaneously buried induction coil in the rabbit which was activated by a primary held above the head. Gengerelli (1950) employed a radiofrequency apparatus in the rat, with an externally placed antenna. Verzeano and French (1953) used an external remote receiver with a transistor circuit. Recently

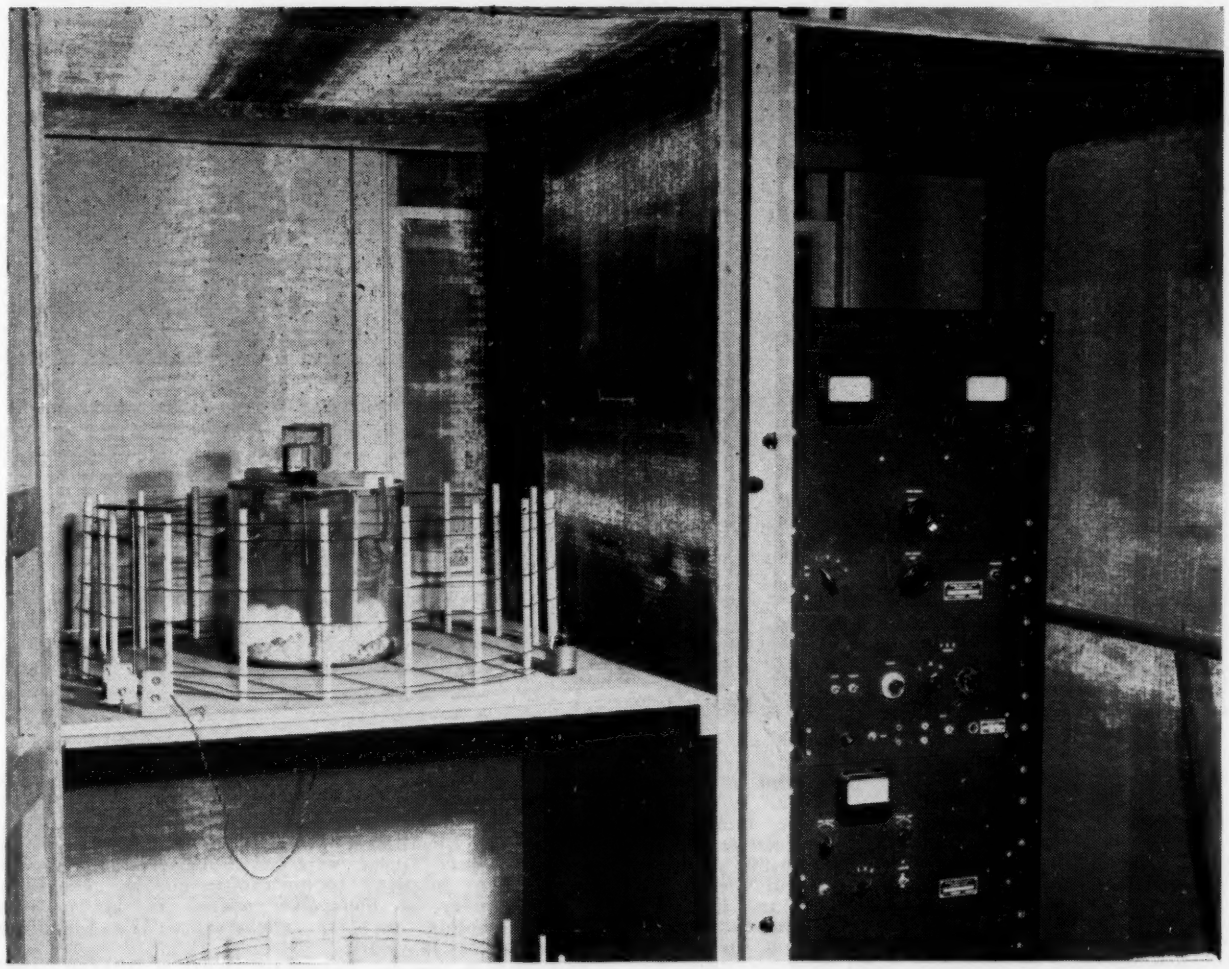

Fig. 1
One of 4 compartments of enclosed cage; upper section contains rats. Transmitter in compartment on right. The screen doors are open to permit photography.

1 Present address: Department of Medicine, University of Oregon Medical School, Portland, Oregon.

Lafferty and Farrell (1949) have described a subcutaneously buried radio receiver unit for chronic nerve stimulation. This has been adapted by Hume (1953) for stimulating the hypothalamus of the dog.

A further modification of the apparatus of Lafferty and Farrell has been developed by us over the past three years for chronic stimulation of the rat hypothalamus. Although certain flaws are still present in the system as currently used, it is felt that its development has proceeded to a point adequate to make its description of value to other investigators who may be interested in this type of equipment.

the transmitter is carried to 6 individually tuned circular transmitter antennas. Each antenna is 22 inches in diameter, and consists of 7 parallel radiators (fig. 1). The transmitter and antennas are housed in a four compartment box, 15 feet long, 3½ feet wide, and 7 feet high. Each compartment has a separate full length door and each is completely enclosed and shielded by copper screening. The transmitter occupies one compartment. The other three compartments are divided into an equal upper and lower section by a shelf of ½ inch plywood; each of these sections contains one of the

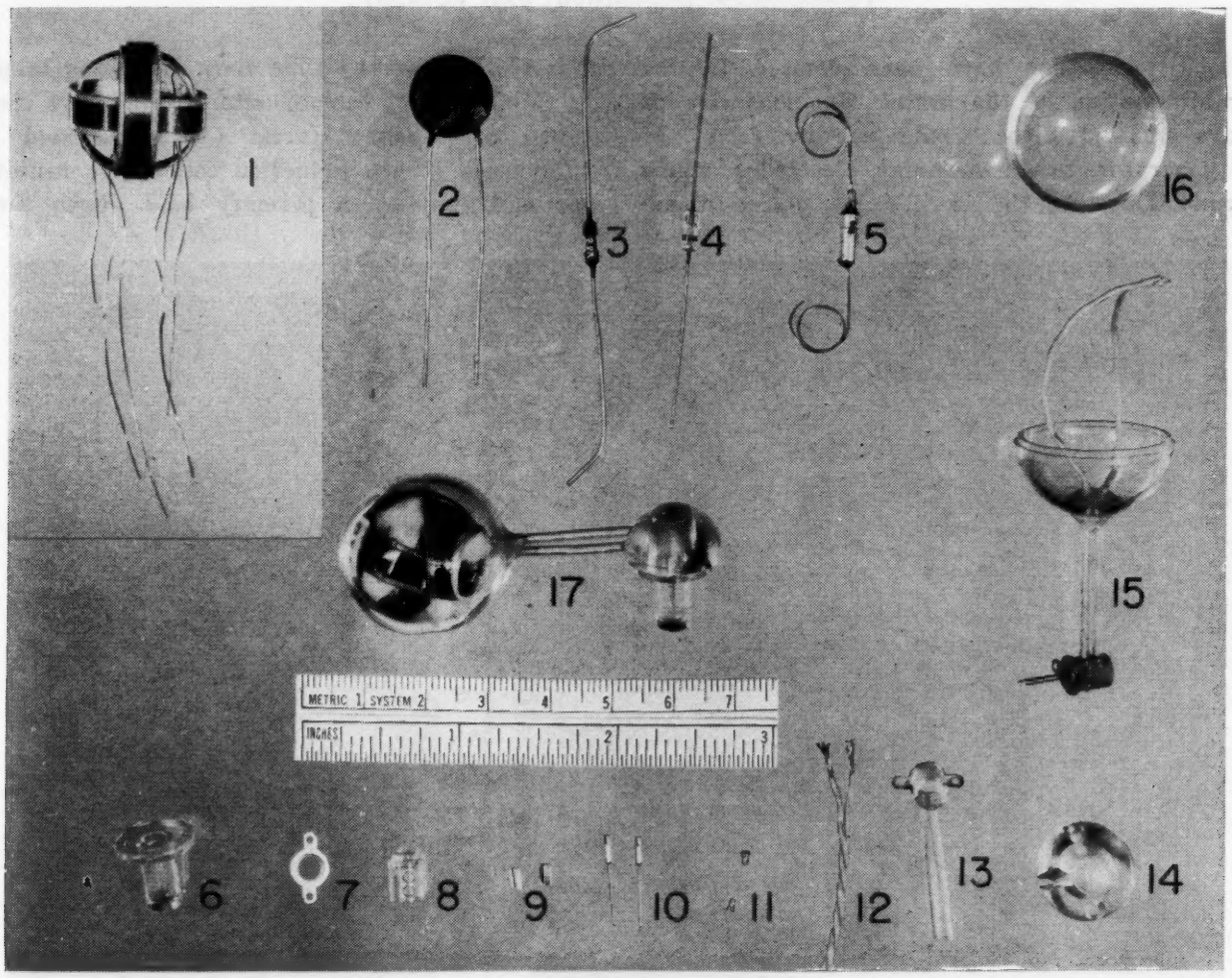

Fig. 2

Illustration of parts and steps involved in manufacture of radio receivers. 1. Radiofrequency pick-up loops. 2. Resonant frequency capacitor. 3. Time decay resistor. 4. Rectifier, 1-N-95 diode. 5. Biphasic capacitor. 6. Electrode protective cover, lucite. 7. Punched silver yoke. 8. Lead transfer housing, lucite. 9. Silver electrode clamps-between electrode and conductor. 10. Electrodes, platinum-iridium. 11. Silver cranial attachment screws, number 00-90 size. 12. Stranded silver tinsel wire used between electrodes and receiver loops. 13. Sub-assembly of the lead transfer housing showing lucite tubing guides. 14. Protective hemisphere for transfer housing, lucite. 15. Sub-assembly of electrodes sealed in place with dental acrylic resin. 16. Second lucite hemisphere to complete receiver enclosure. 17. Complete receiver with protective hemisphere and electrode protective cover in place.

MATERIALS AND METHODS

1. *Radio transmitter.* This is essentially a standard 200 watt output continuous wave transmitter operating at 14 MC and keyed by an automatic pulsing device which permits regulation of frequency and duration of the pulse. The signal from

antennas. A single pick-up loop identical to those used in the receiver units is affixed to the bottom of each plywood shelf and in the center of each transmitting loop. Leads run from each pick-up loop to a plug at the periphery of each section so that the output from each antenna can be individually

monitored on an oscilloscope. A circular glass cage or individual plastic cages, each with perforated plywood covers, can be placed within each antenna. The plastic cages are standard rectangular mouse cages, 11½ inches long, 7 inches wide and 5 inches high, and can comfortably hold one adult rat each. Six plastic cages can be placed easily in two tiers in each section, giving a total capacity to the apparatus of 36 rats.

2. *Manufacture of receivers.* The steps involved in making the radio receivers are illustrated in figure 2. A silver plate is stamped out with a die, two symmetrical wings with holes for the screws and one large hole for the lucite electrode carrier being included (7). The fabricated, hollow lucite unit (8) is then pressed in place and the platinum-iridium electrodes (10) inserted. The electrodes are crimped separately to tinsel-wire leads (12), each lead passing from the lucite unit through a flared polyethylene tube (13) to the two-piece plastic ball (15 and 16). The open lucite cup is then sealed tightly with acrylic resin.

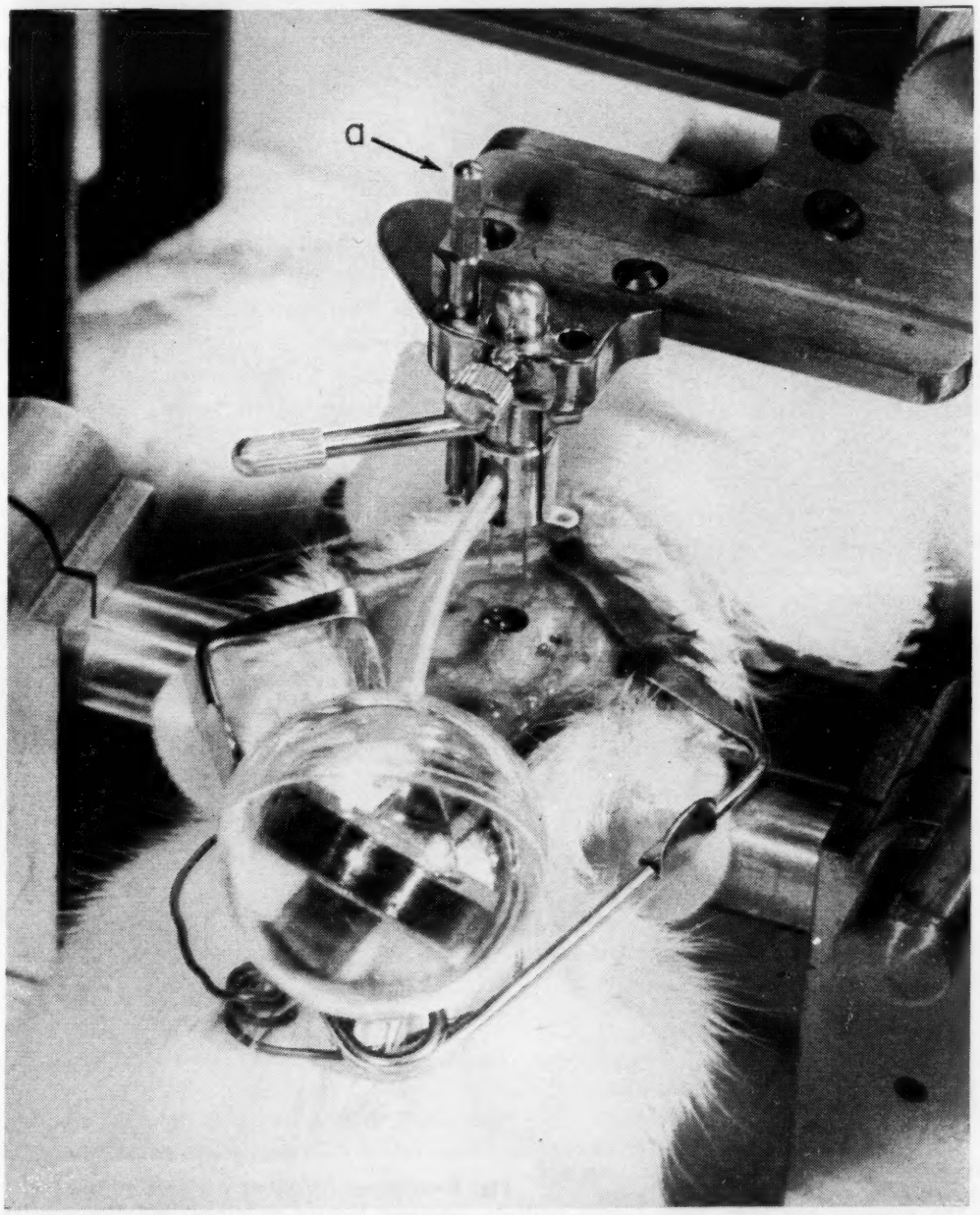

Fig. 3

The three holes having been drilled in the skull and the screwholes tapped, the receiver unit is placed in its special holder and alignment of the screwholes in the silver yoke made with the bar (a).

The plastic ball containing the pick-up antenna is one inch in diameter. Three antenna loops containing 16 turns each of number 36 enameled copper wire are placed at right angles to each other (1) in the ball and connected in series through a germanium diode (4). A condenser (2) is connected across the coils to resonate the circuit and at the same time keep RF from reaching the electrodes. A

biphasic pulse can be obtained by using a 0.1 to 1.0 microfarad coupling condenser (5) placed within the plastic ball.

When the pick-up loop is in place and tests out correctly, the leads are sealed into the ball with acrylic resin and the two halves of the ball sealed together with chloroform and lucite cement. The electrodes are insulated by dipping into diluted lucite cement 3 times and the tips are ground to 60° points.

3. *Insertion of receiver units into the rat.* Animals 200 g. or greater in weight are best utilized for this size unit. The rat is anesthetized with ether. An incision is made longitudinally over the dorsum of the skull, extending from just behind the eyes to the upper cervical region. The galea is incised along the muscle border and scraped free from the dorsum of the skull. The animal is placed in a special stereotaxic instrument (Greer *et al.* 1955) which has been fitted with a hardened steel template for drilling holes exactly the same size and distance apart as are the screw holes and central lucite plug of the receiver unit. A ''rest'' to maintain a vertical position of the dental drill used to make the holes is also affixed to the stereotaxic instrument.

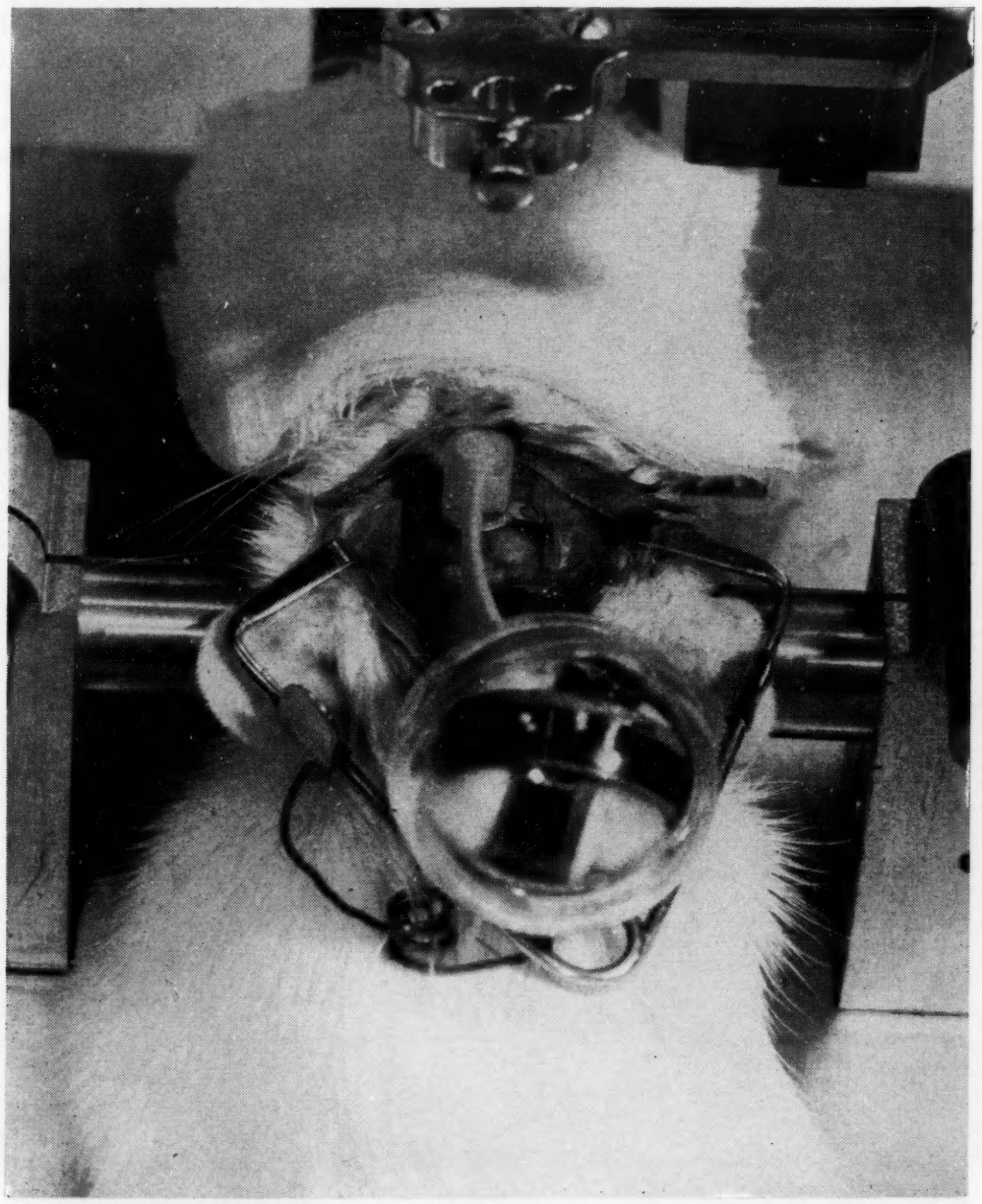

Fig. 4
The receiver has been racked into position, screwed tightly in place and the special holder withdrawn.

A ''pointer'' is placed in the central hole of the template and positioned over the dorsal median sagittal suture at a previously determined position anterior to the ear bars. The rostro-caudal and lateral movements of the stereotaxic instrument are then locked in position. The template is moved down onto the skull, locked in position, and the three holes drilled through the skull with steel drills of

the proper size fitted onto shafts the size of a dental burr and equipped with stops to prevent too deep penetration of the brain. The two lateral screw holes through the bone are threaded with a steel tap.

The radio receiver unit is placed in a special holder and secured in the central opening of the template so that when the unit is lowered to the top of the skull the electrodes will go through the central hole in the skull in the proper position and the screw holes through the silver plate will also be positioned correctly over the holes in the bone (fig. 3). The depth of the electrodes in the skull is determined by fixing their length at the time the receiver is assembled. With the receiver unit in place on top of the skull, small silver screws are placed in the screw holes and the unit secured in place. The holder is released from the unit and the assembly raised leaving the receiver unit securely attached to the skull (fig. 4). A molded plastic hemisphere is placed over the top of that portion of the unit attached to the skull so as to prevent the sharp edge of the unit from eroding the skin. The ball containing the pick-up loops is placed between the scapulae. The skin is then closed by skin clips (fig. 5) and the rat is given a subcutaneous injection of 10,000 units of penicillin.

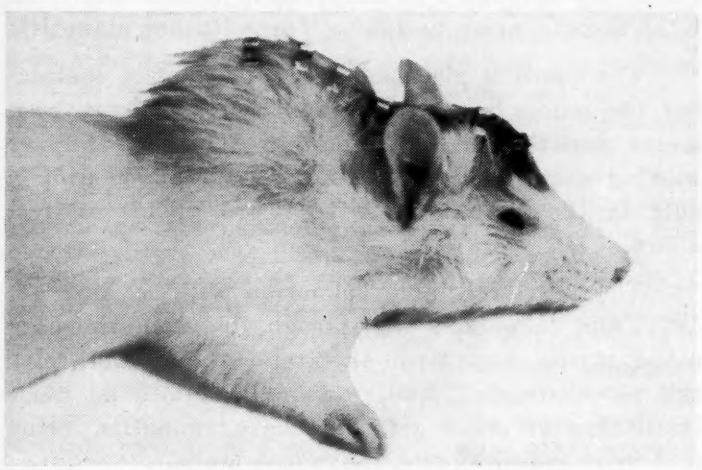

Fig. 5
Rat at completion of operation. Wound closed with skin clips.

The animal is removed to an isolated cage and at least 24 hours are allowed for it to recover from the acute phase of the operation. The rat is then placed in the glass or plastic cage and stimulation with the transmitter begun.

Using either a square or biphasic 2 msec. 60 cycle pulse with stimulation being carried on chronically for 5 min. every half hour, the animals can be carried for at least two to three weeks without appreciable gain in the threshold of response to stimulation. There is little difficulty with breakdown of the skin over the plastic ball or over the hemisphere on the head.

The rats ordinarily begin to respond by increased activity or other external evidence of stimulation when approximately 0.5 - 1.0 V. is developed between electrodes placed in the hypothalamus. The impedance in the rat has been calculated as between 5 and 10,000 ohms.

Although bipolar electrodes 3 mm. apart are currently used in most of the receiver units, other distances probably would be just as satisfactory. It is also possible to build a coaxial electrode in the unit to localize more discretely the area of stimulation.

SUMMARY

Apparatus for chronic stimulation of the brain of the rat by radio-frequency transmission is described. This method of stimulation allows complete freedom of movement of the animal during and between the periods of stimulation.

Kenneth T. Bolen, Instrument Maker, National Institutes of Health, assisted in the project by his ingenuity in the construction of various parts of the apparatus. Leo Rainville, Electronics Engineer, designed the pulse generator and improved the receiver design. We are indebted to Dr. David M. Hume for valuable suggestions and advice in the design of the apparatus.

REFERENCES

GENGERELLI, J. A. and KALLEJIAN, V. Remote stimulation of the brain in the intact animal. *J. Psychol.*, **1950**, *29*: 263-269.

GREER, M. A., MENCKEN, C. and BOLEN, K. T. A modified Krieg stereotaxic instrument for producing intracranial lesions in the rat. *Proc. Soc. Exp. Biol. Med.*, **1955**, *89*: 480-481.

HARRIS, G. W. Electrical stimulation of the hypothalamus and the mechanism of neural control of the adenohypophysis. *J. Physiol.*, **1948**, *107*: 418-429.

HUME, D. M. The neuro-endocrine response to injury: Present status of the problem. *Ann. Surg.*, **1953**, *138*: 548-557.

LAFFERTY, J. M. and FERRELL, J. J. A. technique for chronic remote nerve stimulation. *Science*, **1949**, *110*: 140-141.

VERZEANO, M. and FRENCH, J. D. Transistor circuits in remote stimulation. *EEG Clin. Neurophysiol.*, **1953**, *5*: 613-615.

Reference: GREER, M. A. and RIGGLE, G. C. Apparatus for chronic stimulation of the brain of the rat by radiofrequency transmission. *EEG Clin. Neurophysiol.*, **1957**, *9*: 151-155.

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ANNOUNCEMENT

THE BOARD OF QUALIFICATION OF THE AMERICAN ELECTROENCEPHALOGRAPHIC SOCIETY

The last meeting of the board was in New York City, on June 13, 1956, and the term of Chairmanship of Dr. James O'Leary, expired with this meeting.

The new chairman elected was:

Dr. Robert S. Schwab
Massachusetts General Hospital
Boston 14, Massachusetts

Dr. John Knott agreed to continue as secretary; his address is:

Psychopathic Hospital
University of Iowa College of Medicine
Iowa City, Iowa

The other three members of the board are:

Dr. Francis Forster
Georgetown University
Washington, D.C.

Dr. Curtis Marshall
Johns Hopkins Medical School
Baltimore, Maryland

Dr. A. Earl Walker
Johns Hopkins Medical School
Baltimore, Maryland

Requests for application forms or other information should be sent to the chairman at the address above.

At the 1956 examination the following candidates were passed and will be issued certificates:

D. W. Klass
381-C Cropsie
San Antonio, Texas

Frank Morrell
University of Minnesota Dept. Neurology
Minneapolis, Minnesota

Lever Stewart
Montreal Neurological Institute
3801 University Street
Montreal 2, Canada

At the present time the board has examined and certified a total of 19 candidates since 1951 through 1956. Fifty-eight have been issued certificates by qualifying through full membership in the American EEG Society prior to 1950 (''grandfather clause'').

The board is planning to issue a booklet containing the names and addresses of all who have been issued certificates and the date of issue. Anyone wishing a copy of this booklet should please drop a note to the chairman of the board at his address above.

The next written examination will be May 18, 1957, and candidates who are eligible and who have satisfactorily completed the application form, with the payment of $25.00, can be examined at their institution or other activity, the examination being sent to an approved and designated proctor.

It is planned to have the oral and practical examination for those who have successfully passed the written examination during the latter part of October 1957, somewhere in the midwest, approximately before or after the American EEG Society meeting in Santa Fe, New Mexico.

SOCIETY PROCEEDINGS

AMERICAN ELECTROENCEPHALOGRAPHIC SOCIETY

Tenth Annual Meeting

Hotel Claridge, Atlantic City, New Jersey

June 15-17, 1956

President: Dr. John R. KNOTT
Psychopathic Hospital, Iowa City, Iowa

President-elect.: Dr. Robert S. DOW
1010 Medical Dental Building, Portland 5, Oregon

Secretary: Dr. J. K. MERLIS
150 S. Huntington Ave., Boston 30, Massachusetts

Treasurer: Dr. Peter KELLAWAY
Baylor University, Houston, Texas

1. Changes in EEG frequency pattern occurring with recovery in mentally disturbed patients. — MARGARET A. KENNARD and ALEX E. SCHWARTZMAN, University of British Columbia, Vancouver, Canada.

Serial EEGs with analysis of frequency patterns have been made on sixty-two patients in a Mental Hospital and on 25 normal subjects of similar age, intelligence and educational achievement. When the frequency patterns of the patients were compared with those of the controls it was found that: (*a*) there were significant differences in rate and composition of EEG between the normal and abnormal subjects; (*b*) within the group of patients those individuals most acutely and most severely disturbed were those having EEG frequency patterns most deviant from that of the normal control group and (*c*) correlation between certain psychological criteria and EEG frequency pattern was also suggested.

When averages of frequency patterns for these groups of subjects were made, these differences remained significant. Differences in degree of variability of frequency patterns with recovery were also found. The most characteristic difference lay in the demonstrated dys-synchrony of frequencies between cortical recording areas, which was very marked among severely and acutely disturbed psychotic patients but relatively less so among individuals entering the Mental Hospital because of difficulties with immediate environment and consequent non-psychotic behavioural difficulties.

Discussion:

Dr. B. K. BAGCHI (U. of Michigan Hospital, Neuropsychiatric Institute, Ann Arbor, Michigan): I would like to ask Dr. Kennard a question. What part do you think extraneous factors played in causing the frequency patterns and in the distribution of the frequency patterns that you showed ?

I have seen plenty of schizophrenics when they come to the laboratory. They are quite distressed or quite disturbed. What you see at that time is often a disturbance pattern which may disappear at the second or third EEG. In other words, a situation or habituation factor has to be reckoned with. And so I am wondering whether this improvement that is suggested is an intrinsic improvement or improvement of the disturbance pattern due to the habituation to the test situation in the second or third EEG.

PRESIDENT BICKFORD: I should like to make a comment, if I may.

These results certainly interest me a great deal because of the resemblance of some of these frequency effects to what Sem-Jacobsen and his coworkers have found in depth recordings from psychotic patients. No one knows the significance of these slow waves in the depth but they would seem to be related to Dr. Kennard's findings. During periods of hallucination and agitation, he pointed out that the depth electrogram of certain patients changed considerably. However we have to be sure both in the depth studies and possibly with these studies, that some of these effects are not secondary to a very disturbed physiology that is taking place in these patients.

DR. IRA S. ROSS (South Orange, N.J.): My experiences stem from work at the New Jersey State Diagnostic Center at Menlo Park, N.J. In the last six or seven years I have read about 4,000 records of children who were referred there only because of their behavioral disturbances.

We do a certain amount of service at the Diagnostic Center for a number of out-patient State Mental Hygiene Clinics. The out patients are sent into the laboratory because they have been thought to have some organic cerebral disorder accompanying or underlying their behavioral disturbances. The in-patients are there purely because their behavior is too difficult to manage outside of an institution. Every child that comes as an in-patient has an EEG taken. I read about 20 to 30 records a week. About 10 of them come from the outside and about 20 of them are in-patients.

Unfortunately, we have no frequency analyzer, but it has been my experience that from week to week over the years, the in-patient population presents monotonously normal EEGs. Where pathological activity is seen, for the most part it is seen in the select group of out-patients that has been spotted either by psychometric testing or the referring clinician as having organic cerebral disorder.

The question we are at a loss to decide is how much of what appears to be regularity in the visual test would show as irregularity when analyzed. Of course, I have no answer to that. However, I believe that mechanical analyzers can include EEG frequency artifacts that would be eliminated in ordi-

nary visual reading. Wave forms that might stand out recognizably as artifacts in ordinary tracings will only be recorded as a frequency count in the analyzer records.

DR. KENNARD (*closing*): No, Dr. Bagchi, we cannot see these things in the EEG at all without a frequency analysis. At least, I can't. I have tried reading EEGs and predicting which ones would show discordant frequency patterning and which would not, and have found it impossible.

In fast activities, particularly, neither you nor anybody else can tell whether these are the very well-coordinated ones, "low-voltage — fast" ones, with alpha knocked out, or whether they are in the very discoordinated group.

Thirty per cent of our subjects had abnormal EEGs in that they had increased sensitivity and some degree of paroxysmal patterns in relation to hyperventilation.

All patients were completely cooperative, entirely able to take the Rorschach tests, Wechsler Bellevue and various other tests which we gave. They were not patients who were climbing up the walls. They were not patients who had to be kept isolated. They were patients who were in far less disturbed states than those usually seen in mental hospitals. About half were voluntary committals.

I would be inclined to think, with Dr. Bickford, that this is a change which would very probably be picked up in deeper recordings to a more marked degree than on the surface.

I would think that this must have something to do with the activating system which shows the influx, the importance in pattern of the cortex throughout its various areas, and I think that the thing to remember is that this demonstrates the dys-synchrony of frequencies between areas.

I have a long analysis, with slides, which I didn't show you, in which we show patients with very mixed-up inter-area graphs. But, also, we have recorded and graphed 10 consecutive or 8 consecutive frequency patterns from one given area, and there is no distortion in 8 consecutive graphs from a single area.

The last speaker, I am not quite sure whether he asked me a question. I have not worked much with young children as yet. My impression is from the few that we have done that we will get some very interesting relationships in these inter-area frequencies with children also.

2. Effect of atropine and scopolamine upon electroencephalographic changes induced by electroshock. — GEORGE A. ULETT and MARGARET W. JOHNSON, Washington University and Malcolm Bliss Psychiatric Hospital, St. Louis, Missouri.

This is a preliminary investigation of the effects of atropine and scopolamine upon the alteration of brain wave pattern that characteristically accompanies a course of electro-convulsive treatments. Atropine was administered to 7 patients in daily doses of from 1 - 5 mg. Scopolamine was administered to 5 patients in doses of 1 - 3 mg. daily. EEG's were taken at rest and at intervals throughout and after completion of a course of 12 ECT treatments. It was found that both of these agents clearly blocked the occurrence of slow waves usually seen with ECT. In cases where the drug was continued for a week or more after termination of shock treatment, marked slowing of the EEG did not appear. If the drug was discontinued within 1 - 2 days after the course of shock treatment slow high voltage activity could suddenly appear. Comparisons are made with the EEG's of patients receiving ECT without such medication.

One patient received two courses of ECT and was able to serve as his own control. Throughout the first course he received atropine and showed minor alteration in the EEG. The second course was given without atropine and marked slowing occurred. Clinical observations and the possible significance of findings are discussed.

Discussion:

DR. RICHARD P. SCHMIDT (Divisions of Neurosurgery and Neurology, University of Washington School of Medicine, Seattle, Washington): The group working with Dr. Ward in Seattle has been interested in the effect of anticholinergic drugs in a wide variety of conditions associated with depression of awareness or consciousness. These effects were first demonstrated in cerebral concussion. At times in the human as well as in the animal, administration of anticholinergic drugs will produce a dramatic reversal of a depressed state of consciousness. It has been evident to us that this alerting effect may also be obtained in a wide variety of medical conditions not associated with head injury.

Several slides will demonstrate the type of effect that we have observed. The first is from a control EEG of a monkey showing normal patterns. The second slide from an EEG 4 min. after electroshock reveals marked hypersynchronous slow activity. The third illustration demonstrates a marked attenuation of the slowing within 10 sec. after the intravenous administration of atropine sulfate. It is further demonstrated in the next slide that the slowing of the EEG resulting from electroshock in the monkey can be prevented by pre-treatment with atropine.

The next two slides illustrate a somewhat different state. These are EEG's from a patient developing a depressed state of consciousness several weeks following an hypophysectomy for metastatic malignancy. The basis for her coma was undetermined but it was not associated with any known structural lesion or chemical imbalance. The control EEG shows a marked degree of slowing at which time the patient was barely responsive to maximal pain or shout stimuli — a little groan or a little movement now and then. Twenty-five minutes after the administration of 0.5 mg. of scopolamine intravenously, the EEG shows a considerably more rapid background rhythm. Whereas previously the maximum rate was 4 per sec., this shows a background frequency of 8 per sec. This decrease in slowing was correlated with an increased alertness of the patient who would respond to her name and answer simple questions.

I would be of the feeling that in these instances, the effect of atropine is most probably on conduction in diffusely projecting neuron systems in the brain stem. Some of the effects of ECT may result from the distribution of currents in this area.

DR. GEORGE A. ULETT (*closing*): In response to Dr. Schmidt's question, we had one patient who had frontal slow activity present in her resting record. When she was given shock treatment, with atropine, there was at times on the day of treatment, diffuse slow activity all over the record. Recordings taken at times one day removed from the treatment showed only normal activity.

I appreciate the discussion of Drs.' Schmidt and Ward. I am puzzled by their statement that atropine

seems to increase alertness, and combat impairment of consciousness, because in our patients who were receiving atropine and scopolamine and had psychological testing, it was our observation that with both drugs, but especially with scopolamine our patients were less alert. Some of them were so drowsy that we had difficulty in arousing them and bringing them down to the laboratory. This is one of the reasons we used atropine rather than scopolamine, but even in the patients on atropine there was some impairment of alertness and consciousness during treatment.

3. Individual differences in the EEG effects of chlorpromazine. — W. T. Liberson, Veterans Administration Hospital, Northampton, Mass.

Last year we reported that moderate dosages of chlorpromazine (400 mg. daily) produced a slight, if any, shift in the background frequency. When it did, a slightly slower frequency was observed. In a recent report, we described a marked shift toward theta rhythm in some schizophrenic patients who were receiving Reserpine (7 mg. daily) or combined Reserpine and chlorpromazine therapy. The present report concerns 14 schizophrenic patients receiving increasing dosages of chlorpromazine (up to 800 mg. daily over a 2 month period). With these high dosages, there were 3 patients whose basic activity shifted from 9-10 per sec. (before treatment) to 3.5 to 6 per sec. at the end of the treatment. On the other hand, some patients have not shown any significant change under the same conditions. This shows considerable individual differences in the effects of high dosages of tranquilizing drugs. These effects should be determined in each patient submitted to this therapy in order to evaluate the mechanism of the tranquilizing effects in specific cases.

4. Psychological functioning of aged individuals with normal and abnormal electroencephalograms. — Ewald W. Busse, Robert H. Barnes, Edward L. Friedman and Edward J. Kelty, Duke University, Durham, North Carolina.

Our studies in the processes of aging, begun in 1950 and dealing with individuals of 60 years of age and over, have indicated that a sizable proportion (approximately one-third) present electrographic disturbances over the temporal regions, predominantly on the left and anteriorly. The initial findings were based on a group of 145 functioning (i.e., non-hospitalized) elderly individuals in Colorado. Subsequently we have confirmed these findings in a similar group in North Carolina.

This report will summarize these findings, and review the literature concerning the etiology, locus and possible significance of the focal temporal EEG abnormalities. In addition, the results of comparisons between elderly individuals with such disturbances and without them will be presented. Specifically, comparisons of psychological functioning based on certain of the Wechsler-Bellevue and Wechsler Adult Intelligence Scale subtests will be reported. Further, a measure of personality functioning — the Fisher Maladjustment Scale — based on Rorschach evaluation of these individuals, gives us further valuable data for comparison, which will be presented.

Briefly stated, we cannot differentiate between functioning elderly individuals with focal EEG changes and those with normal records on the basis of these procedures. The findings in functioning elderly individuals with diffuse EEG disturbances and mixed focal and diffuse disturbances will also be presented and compared. The report will conclude with a tentative discussion of the implications of these findings.

Discussion:

Dr. Jerome K. Merlis (Boston V. A. Hospital, Boston, Mass.): Did you make an attempt to separate the fast from the slow records? On many occasions we have found there was a difference between readings and psychological changes but to my knowledge it was not related to a slow record.

My other question relates to the left temporal disturbances. I wondered whether this was just due to handedness rather than to anything else, because in children we have just the opposite.

Dr. Kenneth A. Kooi (Salt Lake City, Utah): I have three questions that come to mind. One is how valid are the Wechsler and Rorschach tests in determining brain damage.

Secondly, I have a question about functioning — functioning in a community. I am wondering about using this as a criterion of normality. It is found that many elderly individuals come to a hospital not because their mental condition is so remarkable but because of community intolerance to the situation.

The third question is in relation to the type of "diffuse" disturbance. Did these individuals show persistently slow basic patterns or intermittent bursts of slow waves?

Dr. Busse (*closing*): We did not investigate slow records versus fast records because we did not feel we had a large enough group to treat statistically.

We had made some attempt to relate handedness to laterality in the focal and mixed groups. Of the 67 people with focal disturbances and handedness that we tested, only 2 were lefthanded. One of these presented left temporal focus and the other bitemporal. So, until a larger group of lefthanded people with temporal focusing can be studied on the project, we cannot say that handedness is not related to temporal EEG abnormalities nor that it is, but at this particular stage, there seems to be little relationship between the two phenomena.

On the validity of the Wechsler and Rorschach in picking up brain damage in patients, there is a large volume of literature on the subject and some people are more successful than others in using them.

There was a comment about how our subjects were functioning. They were taken primarily from the Golden Age Clubs for retired people, such as retired factory members and like workers, and they represented a wide socio-economic grouping.

We too are disturbed about the problem of what do you call a "normal" older person, especially when you find so many deviate EEG patterns, and the only way we felt we could approach this was by trying to sample from as large a number of groups as possible.

5. Electroencephalographic findings in phenylketonuria. — Niels L. Low, James F. Bosma and Marvin D. Armstrong, University of Utah College of Medicine and Utah State Training School, Salt Lake City, Utah.

In phenylketonuria there is an inherited biochemical defect in the normal oxidation of phenyl-

alanine to tyrosine. Affected persons are mentally retarded, usually severely, and many have seizures in childhood. Because this entity has been well studied chemically and clinically, and because control of the chemical aberration has been achieved by dietary means, phenylketonuria lends itself well as a model for EEG studies of metabolic disease affecting the brain.

Eighty-six EEGs were obtained on 19 phenylketonuric patients at ages 7 months to 49 years. Seizure history was positive in 8, most commonly in the form of ''infantile spasms''.

Five patients showed *hypsarrhythmia;* 4 of these were the youngest patients in the group. *Multiple spike seizure foci* were found only in children under 2 years. *Occipital* and *temporal* spike foci were recorded in an age range from 8 months to 13 years. Spikes from the parietal and frontal areas, and larval *grand mal,* were seen in older children and one adult; *14 and 6* per sec. spikes were present in one 46 year old woman. Paroxysmal slow activity without seizure discharges was recorded in one boy. The oldest patient in this series had a *normal* EEG on 2 occasions.

Seven patients had *spike and wave* discharges of frequencies from 3 to 6 per sec.; in 3 children these discharges were very similar to the findings in petit mal epilepsy.

EEG and seizure improvement on a phenylalanine restricted diet was parallel to and usually more striking than other clinical changes.

6. The significance of disagreement between EEG, clinical and pathological findings. — B. K. Bagghi, Leopold Liss, Kenneth Moore and E. A. Rodin, University of Michigan, Ann Arbor, Ypsilanti State Hospital, Ypsilanti, Michigan.

The purpose of this report is to stress some of the discrepancies or negative and indeterminate correlations between EEG, clinical and pathological findings. Such disagreements are frustrating and are usually passed up as being due to differences in methods used in the respective fields and to biological variations. However, they may stimulate a search for hitherto undiscovered clues that may more satisfactorily explain some of them. Change or modification of technique, investigatory approach and interpretational thinking will then be in order.

Thirteen psychiatric cases (47 to 101 years) with EEG and without brain tumor, epilepsy and gross evidence of C. V. A. were selected out of 544 autopsies. Nine showed normal EEG pattern but moderate to most profound degenerative, presenile or senile changes. This group included a 101 year old patient who had a normal EEG. Normal EEG was seen in a case of verified Pick's disease with gross mental deterioration. Silver impregnation and H. E. findings of cortex, hypothalamus, dorsomedial nucleus of thalamus and brain stem of these cases will be reported.

Conversely, marked spike-waves characterized the two EEG's of a girl (I.Q. 137) without personal or familial epilepsy. Clinically, she developed sibling rivalry and stopped talking without other behavior changes. Extensive study by three clinical departments produced no evidence of epilepsy.

A psychiatric patient with profound agitated depression but without any neurological signs or symptoms showed marked bitemporal spikey theta paroxysms.

Marked spike-waves developed in the right temporal area in the second post-operative EEG (6 months), which disappeared later, in a case that had pulmonary valvulotomy with clinical improvement. The significance of these and other cases will be discussed.

Discussion:

Dr. Milton M. Parker (White Cross Hospital and Ohio State University, Columbus, O.): All electroencephalographers who have worked with emotionally distressed patients have seen paroxysmal activities in the period of disturbance which, as the clinical psychiatric upheaval subsides, are modified or disappear.

This suggests that the EEG is simply not a changeless pattern. Rather it is subject to the effects of emotional stimulation; and this is something about which we electroencephalographers do not yet know enough.

With regard to ''normal'' aging and the electroencephalographer's criteria of abnormality, it is my estimation that the data are too crude to provide us with correlations which might be significant. However considerable refinement is at hand.

Dr. David R. Talbot (Pacific Palisades, California): I think Dr. Bagchi's paper is very interesting and has brought to mind that the EEG cannot be too easily understood. As one who has worked with it for fifteen years, however, I feel that the EEG is still a useful laboratory method and it should not be discarded.

Some one individual said something here about psychiatrists looking to the EEG as a touchstone to solve all their questions. I am a psychiatrist and I do not feel that it does that. Still, you can usually find some good neurophysiological reason behind the failure of EEG to show a proper correlation with the clinical, pathological and neurological findings in any given case.

I wish to say a word about those mental defectives who often show a perfectly normal EEG, a fact which is quite disturbing to some clinicians, but this is not hard to understand for if a count of the number of neuron cells in a square millimeter of this brain is made as against one from the same area of a normal child's brain, it is found that the cells in the defective cortex are much fewer in number, hence, they cannot perform their function as does a normal brain. Yet the few cells that are in the defective's cortex do discharge their electric potentialism in a normal rhythmic manner and hence give a normal EEG recording. However, in the vast majority of psychiatric and neurological cases that I have studied there is a good correlation between the EEG clinical and pathological findings especially if sleep records are used to activate the abnormality that points out the focus of the brain defect. I think it is a swell idea to point out that there is an occasional case in which the EEG is puzzling, but the more we learn about EEG, the more we will be able to help psychiatrically neurologically sick people to get well and back to work.

In conclusion, I think we appreciate Dr. Bagchi's statement that there are occasional cases which at first sight seem to show disagreement with the clinical picture, but let us not publicize these exceptions when we have a new branch of medical science that is

helping us to understand the neurophysiology of the ill patient.

DR. ROBERT S. SCHWAB (Boston): I don't see any reason for being on the defensive. I think we can see that we have to study a sick person with a number of different tools and if they do not agree, we have got to look at the individual and his disease more carefully.

I think this is a fine piece of work and I congratulate Dr. Bagchi.

DR. BAGCHI (*closing*): I am not the one to throw the EEG out the window, as you very well know. I would say that we know more about the relationship between the EEG and clinical syndromes so far than we do about the EEG itself.

I agree with the discussant that EEG is just one of the tools.

7. "Isolation", as opposed to injury or ischemia, as the important factor in the supersensitivity of isolated cortex. — FRANCIS A. ECHLIN, New York, N. Y.

In 10 monkeys a frontal lobotomy was performed through a stab wound in the dura. Six to 10 months later the dura was widely opened and electrocorticograms were made with multiple bipolar recordings. Following the topical application of acetylcholine, 0.2 to 0.75 per cent to the cortex, prolonged rhythmic wave and spike (epileptiform) discharges occurred selectively from the isolated frontal lobe. At a given distance from the lobotomy incision the degree of injury or of ischemia was presumably essentially the same over the "isolated" area as over the non-"isolated" cortex. However, the discharges described occurred only from "isolated" cortex indicating that the "isolation factor" was responsible. Lobotomy, as demonstrated, causes a change in the physiological chemistry (a supersensitivity) of the cortex in the isolated frontal lobe was probably also of partially isolated cells at a distance, for instance in the hypothalamus. It is suggested that this supersensitivity of "isolated" cells may be a factor in the clinical effects of lobotomy.

8. Conditioning of an abnormal hypersynchronous discharge. — FRANK MORRELL and ROBERT NAQUET, Minneapolis, Minn. and Marseille, France.

A previous report before this Society dealt with the electrical signs of a repetitive conditional response of cortical cells. In the past year we have studied the effect of focal epileptogenic lesions and of analeptic drugs upon this response in the cat, rabbit and monkey and have observed several other forms of conditional response. One of these was a clearly defined abnormal hypersynchronous discharge.

In a group of animals (cat, rabbit, monkey) with unilateral occipital lobe aluminum hydroxide lesions, it was found that photic stimulation at low frequencies elicited not only a typical "driving" response but also a prolonged after discharge localized to the abnormal occipital region. With continued stimulation, the after discharge spread to other areas and became independent of the specific frequency of the flicker. Soon a high voltage, diffuse, paroxysmal hypersynchronous discharge was elicited with each presentation of the stroboscopic light. The frequency of the discharge, although apparently influenced by the flicker frequency, seemed more determined by the condition of the animal and the resting electrical pattern.

After several paired trials, a low tone stimulus which previously had no effect on the EEG, was noted to elicit this response. The usual criteria of conditioning, i.e.: differentiation, extinction and spontaneous restoration, were noted. The effect of barbiturates and of Metrazol will be demonstrated and some implications of these observations opened to discussion.

Discussion:

DR. YOSHII: I used the same method as Dr. Morrell and. Dr. Naquet, except for two points. I used intact cats and recorded not only cortical but also subcortical EEGs. Electrodes were permanently implanted. My conclusions are as follows:

1. The frequency specific repetitive response (Morrel and Jasper 1955) or the conditioned brain waves at the same frequency as flicker stimulus appeared more frequently and more importantly in midbrain reticular formation than occipital cortex.

2. When these specific waves appeared in occipital cortex they were believed to be transmitted from the origin in the brain stem reticular system.

9. The pacing of EEG potentials of alpha frequency by low rates of repetitive flash in man. — JOHN S. BARLOW and MARY A. B. BRAZIER, Massachusetts General Hospital, Boston Massachusetts Institute of Technology, Cambridge, Mass.

With slowly repeated flashes a cortical response can frequently be detected in the EEG of man. Competing potentials usually mask all but the initial component of the evoked response. Techniques for averaging many of such responses emphasize those components whose incidence is related and time-locked to the flash, whereas potential fluctuations that have no time-relation to the flash are averaged out.

For the work presented here an electronic circuit has been used that was designed and constructed by one of us (J.S.B.) in collaboration with the Research Laboratory of Electronics at M.I.T. as a part of an analog correlator for brain potentials developed in the laboratory of Prof. W. Rosenblith.

Results obtained by this type of crosscorrelation of the EEG with the stimulus at flashrates of approximately 1 per second will be shown. Some evidence will be presented that the following events, having fixed latencies from the flash, may, by analogy with animal experiments, be identified in the EEG of man: an occiput-positive response probably indicating impulses approaching in the radiations and invading the cortical cells by axosomatic synapsis; a long occiput-negative wave, representing invasion of the apical dendrites; and then a series of oscillatory potentials (suggesting, again by analogy with animal experiments, a fluctuating level of dendritic potential under axodendritic influence from the diffuse projection system).

These oscillatory potentials are masked in the usual recording. It is now possible to give their characteristics. They have periodicity, their frequency lying in the alpha range, but their phase is linked to and paced by the flash. Their frequency does not appear to be harmonically related to the flashrate. These findings will be discussed.

10. Direct current recordings of recruitment responses in the cat evoked by massa intermedia stimulation. — Robert Cohn, U.S. Naval Hospital Bethesda, Maryland.

Utilizing amplifiers capable of recording direct current potentials it has been shown that during the production of spike-dome activity in man there is a pronounced almost immediate negative shift of the baseline. Because of the constancy of this phenomenon a study was made to determine whether the cortical recruitment response to massa intermedia nuclei stimulation (electric) in the cat, which has a morphological similarity to human spike-dome activity, would have similar direct current properties. The direct current shifts observed over the gyrus proreus following electrical stimulation of the massa intermedia, when present, were positive in polarity; more usually a very slow positive-negative fluctuating potential was recognized. Because of the inability to obtain negative DC shifts from the gyrus proreus it appears that the cortical spike-dome-like activity of the cat is generically different from the spike-dome discharges observed in the convulsive states of man. As a consequence it appears that recruitment activity in the cat, despite certain morphological similarities, can not be used as an experimental model for the spike-dome activity in man.

Discussion:

Dr. J. L. O'Leary: I am by no means in a good position to assess the recruiting aspects of Dr. Cohn's paper. It seemed to me, however, that his most critical slide was one in which his recruiting responses were recorded as positive transients and he had a positive direct current swing accompanying it.

In the rabbit at least we have been able to show both negative and positive components reacting by recruitment. Sometimes in the rabbit in the precentral granular and precentral agranular, you can get positive transients in one instance and negative recruiting in the other.

The significant feature to me of the relationship of the polarity of DC shift is in the fact that in all the work that has been done by Goldring and myself, it has been a rare instance when we have been able to demonstrate a disparity in polarity between transient and direct current shift.

Chairman Kellaway: Dr. Cohn, that sounded like a difficult question. Would you like to answer that first, about the disparity in polarity.

Dr. Cohn: I am unable to understand the precise nature of the interrogatory remark.

Dr. O'Leary: Dr. Cohn, the point is that I have to put what I read in your abstract together with what I heard you say. Now you claim that the spike-dome activity that Jasper has described previously, cannot be, from direct current stand-point, the same as the human spike-dome activity.

The difficulty for me is that I expect the polarity of the transients in your experimental instance to be at variance with the polarity of the direct current change, to prove your point. Is that clear ?

Dr. Cohn: (*closing*): As I noted at the time of the presentation, the slide that Dr. O'Leary has reference to is quite unique ! The major point that I wish to stress is that there is little or no general DC shift in the recruitment response elicited in these experiments. I believe that the relation between the polarity of the transients and the very occasionally observed DC shifts is not critical.

11. Paradoxical inhibitory action of convulsants on evoked cortical activity. — Dominick P. Purpura and Harry Grundfest, Columbia-Presbyterian Medical Center, New York, N. Y.

It has been shown that high frequency stimulation of the bulbar reticular system inhibits cortical dendritic activity evoked by surface stimulation (Purpura, *Science*, 1956). This inhibition which persists for seconds after the stimulus, is further augmented by topical application of strychnine in concentrations sufficient to induce intermittent cortical spiking. The development of intermittent and sustained paroxysms induced by intravenous administration of strychnine or Metrazol is also associated with inhibition of dendritic responses elicited by surface stimulation or antidromic activation of the medullary pyramids in paralyzed, unanesthetized cats.

Examination of orthodromic pyramidal responses evoked by motor cortex stimulation during the intermittent strychnine paroxysm shows a marked facilitation especially of the relayed (indirect) descending activity whereas the interseizure "silent period" is associated with abolition of this latter activity without significant alteration in the direct responses. That these "silent periods" are not associated with "neuronal fatigue" is demonstrated by the return of dendritic responsiveness during the interseizure silence and the facilitating action of d-tubocurarine on the strychnine seizure in concentrations usually sufficient to inhibit all cortical synaptic activity (Purpura and Grundfest, *Fed. Proc.*, 1956). This suggests the operation of at least two factors necessary for the development of the strychnine and Metrazol paroxysm: (1) inactivation of dendritic synapses; and (2) partial blockade of cortical inhibitory mechanisms which is intermittently overcome to produce the electrical "silences".

The facilitation of topically evoked strychnine spikes following high frequency bulbar stimulation suggests additive *inhibitory* effects on dendritic activity of brain stem stimulation and topical strychnine. The possible nature of this combined 'paradoxical' inhibition of evoked cortical activity by the most powerful known convulsant, on the one hand, and an alerting stimulus on the other, will be discussed.

Discussion:

Dr. Liberson (Northampton, Mass.): I was particularly interested in what you said about periods of silence during paroxysmal discharges. We found at first with such discharges that underlying them there was a wave in one direction while during silence it was a wave in the opposite direction. I wonder whether you would care to comment on that.

Dr. Purpura (*closing*): I want to thank Dr. Liberson for his comment.

The opposite shift that you have observed we feel can be observed in the simple recording of dendritic responses in the cortex. When one evokes these by a surface stimulus, one is obviously stimulating both excitory and inhibitory afferents ending on the apical dendrities, and when this occurs one observes first an evoked potential, indicating an excitory ef-

fect, but far outlasting this and developing during the excitory effect is what we believe to be inhibitory effects set up on the dendrites persisting up to 120 or 100 msec., and we feel that the interplay of these excitory and inhibitory effects may contribute to the underlying EEG oscillations.

12. Threshold convulsant levels of analeptic drugs in normal and epileptic monkeys. — JOSEPH G. CHUSID, LENORE M. KOPELOFF and NICHOLAS KOPELOFF, N. Y. State Psychiatric Institute and St. Vincent's Hospital, New York, N. Y.

Studies were made of several analeptic drugs to determine the minimal quantities required to produce clinical convulsions in normal monkeys and in monkeys made chronically epileptic by the application of alumina cream to the brain. Drugs tested included pentamethylenetetrazole (Metrazol), diphenhydramine (Benadryl), tripellenamine (Pyribenzamine), aminourea (Semicarbazide), strychnine sulfate and picrotoxin. Test substances were administered by rapid intravenous or intramuscular injection with intervals of a week or more between individual injections. Comparison of the threshold values for epileptic and normal monkeys indicated that the drug tested and the method of injection were significant variables. Differences in threshold convulsant dosages of epileptic and non-epileptic monkeys were particularly noteworthy with intramuscular Metrazol, intramuscular Pyribenzamine, intravenous Semicarbazide, intravenous picrotoxin and intramuscular picrotoxin. The data suggests that the response to "challenge dosages" (capable of activating clinical seizures in epileptic monkeys only) of certain analeptic drugs may be useful in evaluating the epileptic status of monkeys.

Discussion:

DR. SCHWAB: I think this is a very important technique in evaluating the effect of analeptic convulsives to see the time they take to work. I wonder if Dr. Chusid has tried any intravenous or intramuscular sodium luminal before the injection of these epileptic agents to see if they would protect the animals against seizure.

DR. R. L. MASLAND: Is there a difference in the types of seizures produced by the different drugs used ?

DR. FRANCIS J. MILLEN (Milwaukee, Wisconsin): Do these findings mean that the use of Benadryl and Pyribenzamine in clinical epilepsy in humans is contraindicated ?

I ask the question because many of our epileptic children have allergies and during the hay fever season we give them large doses of Benadryl and Pyribenzamine without seeing any aggravation of epilepsy.

Also, I wonder about using the term "analeptic" for Benadryl and Pyribenzamine. I never thought of those drugs as analeptic.

DR. A. E. WALKER: We have found in giving Metrazol and some of the other convulsants that if the drug was given in clinical doses that the result was somewhat different than if a stated amount of the drug — so many mg. per kg. is given at one time.

Apparently, when the drug is given in small amounts, the initial dose may sensitize a cortical or subcortical centre which, with subsequent administration of the drug will give rise to a fit, whereas if the drug is given in one slug, a certain number of mg. per kg., the threshold may be quite different.

We found, as I recall, in our monkeys with Metrazol that the alumina epileptic animals had a threshold of about .2 cc of a 10 per cent solution of Metrazol whereas normal monkeys had a threshold of 0.5 ± 0.07 cc.

Chairman KELLAWAY: I should like to comment, if I may.

I think the concept of threshold is very poorly applied when we attempt clinically to evaluate the patient as a possible epileptic on the basis of his threshold to convulsant drugs.

The overlap of threshold dosage for the production of spike and wave activity by Metrazol is much too great to be of practical value. Some epilepties activate at 800 mg. or more, while some highly selected normals may activate as low as 300 mg.

Would you care to comment, Dr. Chusid ?

DR. CHUSID (*closing*): We have not tested anticonvulsant drugs extensively in epileptic monkeys. The capacity of drugs to prevent seizures or raise the convulsive threshold to parenterally administered analeptic drugs could be used as an index of anticonvulsive action.

Very little quantitative data exists regarding dosages of analeptic drugs required to produce seizures in monkeys. Metrazol is the only reported drug that has been previously tested to any extent. We have today presented our results with picrotoxin, Semicarbazide, Metrazol, Pyribenzamine, Benadryl and strychnine sulfate.

The type of seizure induced following administration of an analeptic drug depends upon the manner of preparation of the particular epileptic monkey and the administration of the analeptic drug. Focal onset of clinical seizure is frequently apparent in monkeys prepared by application of alumina cream to a single cerebral hemisphere. Focal clinical seizures in such preparations are more apt to occur with dosages close to threshold level, while with larger dosages it may be more difficult or impossible to detect a clinical focal onset. The seizures induced by strychnine sulfate were usually rapid in onset, generalized in type and of severe quality. In normal monkeys, when seizures occurred following analeptic drug administration, they were usually generalized.

The quantities of Benadryl and Pyribenzamine used in these experiments far exceeded the quantities used clinically with humans, and were administered parenterally. Accidental human poisonings, especially in children, with these drugs are characterized by status epilepticus, and are often fatal.

It is my impression that the dosages used by Dr. Walker in his experiments with intravenous Metrazol in monkeys are quite comparable in range to our values obtained with the same method, if the dosages are considered on the basis of mg. of drug per kilogram of body weight. In our experiments, single injections of the test analeptic drug were made at weekly intervals and the threshold quantity as considered to be the smallest amount which induced a clinical seizure.

13. Subcortical responses to focal epileptic discharges in the monkey motor cortex. — G. F. Poggio, M. Ribstein, G. B. Udvarhelyi and A. E. Walker, Johns Hopkins Hospital, Baltimore, Maryland.

Experiments were performed in 10 unanesthetized monkeys (6 Macacus Iris and 4 Macacus Rhesus) immobilized with succinyl-choline chloride (Sucostrin, 20 mg/cc.) and artificially ventilated. A cortical epileptic focus was produced by topical application on the face area of the motor cortex of penicillin (10,000,000 U/cc.) (4 animals) or strychnine phosphate (1 per cent solution), (4 animals). In 2 animals strychnine and penicillin were applied in succession. The electrical activity of the basal ganglia and thalamus was simultaneously recorded on both sides by means of a set of 8 concentric electrodes (0.6 mm. outside diameter) stereotactically oriented.

The epileptic activity in the motor cortex, either induced by penicillin or strychnine, is able to elicit responses in the basal nuclei. The structures particularly involved are the ipsilateral putamen and thalamus. Some responses are also present in the ipsilateral globus pallidus, but no discharges have been recorded from the caudate.

In the putamen a certain amount of trispatial organization seems to be present. The epileptic cortical bursts in the motor face area fire the medial portion of the mid part of the putamen, at the level where the globus pallidus is well differentiated in the medial and lateral portions (AP + 14, AP + 11). Only occasional responses have been recorded frontally to these planes. Posteriorly the putamen seems to respond to discharges in the postcentral cortex.

There is some evidence that the motor arm area projects laterally and superiorly to the face area.

The lateral portion of the globus pallidus close to the above mentioned region of the putamen may also show responses to the cortical discharges, but its firing is less constant and defined than that of the putamen.

The thalamus is involved in its ventrobasal portion but responses are also present more medially in the centromedian nucleus and in the inferolateral part of the medial dorsal nucleus.

The contralateral responses are localized to the putamen, showing the same spatial arrangement as the ipsilateral homologous structures. They seem to be secondary to the involvement of the related cortex and greatly dependent on the type of cortical activity, being much more pronounced during the course of a seizure.

The possible implications of these findings in the understanding of the characteristics of the focal seizure will be described.

14. Electroencephalographic observations on the mechanism of breath holding spells. — Hans Strauss, New York, N.Y.

The interval EEG was normal in 16 or 18 patients with breath holding spells. One patient developed later epilepsy with grand and petit mal seizures. His EEG showed diffuse bisynchronous 3 per cent spike and wave patterns. The EEG of another patient showed unilateral single occipital spikes which disappeared within one year during which the patient had had only very few breath holding spells.

EEGs obtained from 4 patients during breath holding spells showed diffuse high voltage slow activity. One of these patients had very numerous attacks with only short intervals during the recording. After the first two spells his state of consciousness remained disturbed and his EEG abnormal. During this "breath holding status" stimulation of the dazed patient by calling his name was sufficient to induce the next spell. This indicates that no conscious elaboration of the stimulus is necessary to induce breath holding. Also it was evident that disturbance of consciousness and electroencephalographic changes appeared in this and one other patient after only a few seconds of breath holding not sufficient to induce the cerebral dysfunction by anoxia or a disturbance of venous return. One must assume, therefore, that patients with breath holding spells have a faulty cerebral mechanism which makes the unconsciousness appear as a reflex reaction to a variety of stimuli.[1] A comparison with cataplexy induced by anger etc. is made.

Periods of electrical silence were observed three times during the breath holding spells of the patient in breath holding status. They lasted as long as 37 seconds. The possibility of permanent brain damage in patients with severe breath holding spells cannot be denied.

Discussion:

Dr. Daniel Silverman (Philadelphia, Pa.): I'd like to make one brief comment on Dr. Strauss' fascinating observations. He showed in a clinical condition what we attempt to do in our laboratory as an activation procedure. We have patients hold their breath voluntarily following hyperventilation, and in many subjects who can cooperate we see the same kind of EEG slowing. One adult actually held his breath until unconsciousness resulted. EEG slowing is usually more marked in children. The EEG changes that Dr. Strauss demonstrated are primarily due to progressive anoxia and I would agree that repeated severe anoxia is not without danger to a child's brain.

Dr. Strauss (*closing*): Contrary to Dr. Silverman, I do not feel that the clinical and electroencephalographic disturbances can be explained simply by anoxia. Anoxic effects, however, may be superimposed to the primary neurogenic disturbance, as explained earlier.

15. Studies on the cerebral pacemaker. — Robert B. Aird, Bill C. Garoutte and Thomas E. Ogden, University of California, San Francisco, Calif.

A systematic study has been made of the degree of synchronism of normal and abnormal types of brain waves recorded simultaneously over homologous areas of the two cerebral hemispheres. The technique involved high-speed photography with a double-beam cathode-ray oscilloscope capable of detecting time differences of as little as one or two milliseconds. Normal controls and patients with petit mal and gross focal dysrhythmias have been studied.

Normal alpha and beta activity showed a high degree of synchrony in 41 patients. Pseudo-rhythmical variations of synchrony were observed when the degree of synchrony was plotted against time. Simultaneous

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1 The effect of anoxia may later during the spell be superimposed upon the primarily neurogenic disturbance.

recording in the fronto-occipital direction confirmed previous observations in showing the frontal waves to lag behind the occipital.

High degrees of bilateral synchrony were found in the typical 3/sec. wave-and-spike activity of 18 patients with petit mal and in the homologous spiking of 8 out of 9 patients with gross focal dysrhythmias.

The degree of bilateral synchrony, which was essentially comparable in both normal and abnormal patients, suggests a ccmmon central pacemaker. Evidence with respect to the probable site and nature of the pacemaker will be reviewed and mechanisms by which it can be influenced will be discussed. The possibility of central nuclear excitation by unilateral focal lesions was supported by these studies. This will be discussed along with the EEG and clinical significance of the cerebral pacemaker mechanism.

Discussion:

DR. BAGCHI: I am very glad to hear this. We have been doing almost the same kind of observation. I have noticed that in some of the brain damaged cases, with high camera speed — 250 mm. per sec. or 500 mm. per sec. — cortical spikes may be first noticed in one hemisphere, then in the other, homolateral or contralateral to the clinical focus. A fixed lateralization or time relationship may not be present.

DR. AIRD (*closing*): I want to thank Dr. Bagchi. I would like to add one note of warning. I doubt if one is justified in drawing conclusions of the type I have been making on the basis of ordinary recordings. Precise and high-speed recording techniques are required to speak with any accuracy concerning the pacemaker mechanism. Actually, very few people have done this type of analysis. Dr. Cohn, for example, has done a nice study along this line on petit mal. However, I doubt if one should draw conclusions based on tracings obtained by means of the usual ink-writer technique.

16. The "14 and 6 per second positive spike" pattern of Gibbs and Gibbs. — PETER KELLAWAY, F. J. MOORE and NINA KAGAWA, Baylor University College of Medicine, Houston, Texas.

The electrographic pattern described by Gibbs and Gibbs in 1951, which they called ''14 and 6 per sec. positive spikes'', has not received wide acceptance even in terms of it being an abnormal finding. Indeed, it has been variously suggested that it is merely a rectification artifact, that it is a peculiarity of ear-to-scalp recording, and that it represents larval seizure discharge activity of temporal lobe origin. However, very little material has been forthcoming which provides critical data either to support or disprove the concept that this pattern is truly an abnormality or that it has specific pathologic and clinical significance.

The data of the present study are based on analyses of the last 200 cases showing this pattern referred routinely to the clinical laboratories for electroencephalographic examination. Only cases 16 years of age and under are included, because this is the only age group for which we have a significant normal control series. Of 950 normal children studied, both awake and asleep, only 2.2 per cent showed this type of pattern.

The wave form of the discharge is predominantly monophasic, although diphasic and even triphasic forms occur in the 6 per second bursts. When recorded with an indifferent electrode elsewhere on the body, the spike deflection is positive in the occipital and temporal areas where the maximum voltage always occurs. If the electrodes are not too closely spaced, the pattern may be distinguished in scalp-to-scalp recording. The field of the discharge indicates that it arises synchronously over a wide area of cortex and its geometry suggests a deep origin.

The pattern is not itself a seizure discharge but a sign of disorder which may have epileptiform manifestations. Clinical seizures are accompanied by generalized hypersynchronous slow activity of spike and slow wave activity, not by positive spike bursts. The clinical correlates of the abnormality are primarily recurrent paroxysmal episodes of autonomic, pain or behavioral type. Headaches and/or abdominal pain with associated symptoms of dizziness, weakness, pallor, nausea and vomiting were the most common complaints in our series.

This is an important electrographic abnormality having diagnostic significance of about the same order of reliability as the 3 per sec. spike and wave pattern but with an incidence many times the latter.

Discussion:

DR. SAMUEL C. LITTLE (Birmingham, Alabama): I would like to mention a few practical points concerning this dysrhythmia.

First, we have found that in some cases it is best seen in the inter-temporal runs. Inter-temporal. And it may be seen there when it is not seen in any other linkage that we have tried.

Secondly I would like to stress the extreme importance of sleep in the detection of this pattern and the extreme brevity of the discharges. It may appear for only a few seconds in an entire record. We thought that you could not obtain it by awakening the patient and allowing him to go to sleep again but in recent discussion with Mr. Gibbs, it appears that this may have been due to the fact that we did not awaken the patient fully.

The other point is the fact that due to the origin of many of the sleep potentials near to vertex, we found that use of the vertex reference causes a rectified appearance to many of the sleep patterns and for that reason it is probably unsatisfactory for studies of this type of dysrhythmia.

Concerning clinical manifestations, we feel that they have an internal consistency which is difficult to describe. The clinical manifestations are quite heterogenous and best described by the word ''atypical''. Atypical disturbances — atypical pains — atypical automatic disturbances. They cannot be described in any other comprehensive term.

DR. C. MARSHALL (Baltimore, Md.): I just want to bear out Dr. Little's comment that the pattern is seen quite clearly temporo-temporally.

I think for the first three years after this pattern was first described, people were telling me that the reason I didn't see it was because I used primarily scalp to scalp recording; the fact that I saw these patterns quite consistently and well didn't deter the common-reference people from explaining to me why I didn't see them !

The only alteration in the visualization of the 14 and 6 pattern when scalp-to-scalp recording is used, is that the voltage is lower as might be expected with the lesser interelectrode spacing.

DR. FRANCIS J. MILLEN (Milwaukee, Wisc.): We reported on a similar but smaller series of cases in 1953 and 1954. Our findings were the same as those reported by Dr. Gibbs in the original paper in 1951, and they coincide with the findings described by Dr. Kellaway today. Since the time of our initial report, our case number has been enlarged to perhaps a hundred patients and includes both children as well as adults.

Serial EEGs in children over a period of years, demonstrate that the dysrhythmia disappears. On the other hand, serial EEGs done within days, weeks, or months, often show the same pattern of positive spiking, but the localization of the spikes may shift from side to side. The spikes may be found on the right side in one record and then on the left side in another record. We found them mostly in the temporal and occipital areas. However, they are found in parietal and frontal areas as well.

One thing we did was to send our patients to another laboratory with a different machine and a different technician, and we found that the spikes were still present. We have seen these positive spikes in several members of families, in one instance, an epileptic family with four children having dysrhythmia, two of them showed 14 and 6 per second positive spikes.

Finally, on reviewing the history and symptoms of the children patients, we find the symptoms described by Dr. Kellaway today, so characteristic that we often anticipate finding the positive spiking discharges before actually reading the record.

DR. FREDERIC A. GIBBS (Chicago, Ill.): This report by Drs. Kellaway, Moore, and Kagawa is in general accord with our observations, and is most gratifying.

I wish to disagree, however, with Dr. Curtis Marshall when he says that 14 and 6 per sec. positive spikes can be seen as readily in bipolar scalp-to-scalp recordings as in monopolar common reference recordings. This statement is not true and is highly misleading.

17. The EEG in febrile convulsions. — JOHN S. PRICHARD and DOUGLAS MCGREAL, Hospital for Sick Children, Toronto, Ontario.

Electroencephalograms were obtained in 146 children under the age of 7 years, who had convulsions associated with fever. The clinical diagnosis has not been considered and the EEG is correlated with the type of seizure, as in the following three groups.

Group I: Convulsion generalized, duration less than 30 min., age range 6 months to 4 years, not followed by sleep or sequelae, good evidence of rise in temperature, child mentally normal.

EEG either (*a*) normal; (*b*) shows an increased amount of slow wave activity, diffusely. This was present in a few cases, when the temperature was raised at the time of recording. In no case was seizure activity seen.

Group II: Convulsion generalized, but otherwise not conforming in one or more respects to the criteria of group I.

EEG either (*a*) normal (26); (*b*) abnormal (21). The abnormalities recorded included diffuse slow wave activity, asymmetrical slow waves and in 7 instances paroxysmal spikes.

Group III: Convulsion asymmetrical, irrespective of other clinical findings.

EEG either (*a*) normal (10); (*b*) abnormal (21). The abnormalities were of diffuse, or asymmetrical slow wave activity. In one case paroxysmal slow activity occurred and in one case there was voltage asymmetry with spike formations.

The time interval elapsing between the convulsion and the EEG recording appears to be significant in some cases but the numbers are too small to be certain. In group I more abnormalities were seen in records taken within a few hours of the seizure (though even some of these were normal) and these were thought to be due to fever. In group III the abnormalities diminished with time but not in all cases.

It is considered that the finding of an abnormal EEG which can not be attributed to fever, after an apparently febrile convulsion, suggests that the seizure was not a "simple febrile" one and other diagnostic possibilities should be entertained.

Discussion:

DR. SCHMIDT: I would like to direct a few short remarks to a consideration of delta activity which may occur focally following a convulsion associated with fever. A number of these cases were studied in conjunction with Dr. Roseman in Louisville and I believe he would agree with my conclusions.

In children, particularly in the age group with an unstable vascular regulating mechanism, we feel that the process of the convulsion itself may precipitate focal brain ischemia. This in turn may cause focal delta activity in the EEG and a hemi-paresis. The occurrence of these focal cerebral abnormalities was more frequent after prolonged or recurrent convulsive seizures. In most there was rapid resolution, but in some, the neurologic deficit was permanent. We had no evidence that this was due to encephalitis or direct inflammation of the brain.

In Lennox's series, approximately seven and one-half per cent of young children developed focal signs after a convulsion, irrespective of the precipitating etiology. Our experience indicated a somewhat higher incidence.

For several years I have been studying EEG's in children presenting unilateral convulsions associated with fever. In most of the cases, no clinical evidence of encephalitis was found, no changes in the cerebral spinal fluid and usually no unilateral neurological signs. About 50 per cent of those whom we could recheck two or three years after their febrile episode had convulsions without fever. In none of these cases did we find any development of classical petit mal epilepsy. The initial EEG changes consist of unilateral delta activity which we described under the name of convulsive cerebritis. In some cases this unilateral delta activity persists for about a month and one is surprised to find such a gross abnormality while the pediatrician and family consider the child as being perfectly normal.

In reviewing these cases recently, I was impressed by the predominance of abnormality in the parieto-occipital regions, and I would like to ask you if this has been your observation also.

DR. SCHWAB: I would like to ask Dr. Prichard and Dr. McGreal whether it is possible, in their opinion, in a normal child with intermittent seizures normally, whether these can be prevented by being on anti-convulsants regularly or only whenever they have fever.

DR. MCGREAL (*closing*): I should like to thank the discussants for their comments.

I think our experience has been the same as Dr. Schmidt, that most of the ones which showed asymmetries occur in the parietal and occipital regions.

With regard to medication; barbiturates intermittently or continuously. It has been our habit not to use continuous preventive measures in simple febrile convulsions. It is my impression that intermittent use would be ineffective since in many cases the convulsion is one of the earliest manifestations of the infection.

18. Periodic bursts in epilepsy. — PAUL M. LEVIN, Dallas, Texas.

Periodic bursts occur in electroencephalograms of severe epilepsy and represent a severe alteration of cortical-subcortical integration as a manifestation of epileptic deterioration. This concept is suggested by the fact that intensive treatment of the epilepsy with suitable combinations of effective drugs will lead to a restitution of continuous rhythmic electrical activity. Such improvement is concomitant with clinical effects of the treatment. The deteriorative courses is brought to a standstill, and there is a variable improvement in the neurologic picture, with speeding of neuromotor and intellectual processes. Such conditions have hitherto been considered from a neuropathologic viewpoint as degenerative and allied diseases of the brain. The term ''subacute progressive encephalitis'' and various descriptive neuropathologic terms have emphasized disintegrative tissue changes leading to progressive dissolution of cerebral function. If the process of epileptic deterioration is a basic factor in the progressive symptomatology, the clinician has a practical approach to the treatment of these difficult cases.

Gross pathologic observations on advanced cases of this type show a disintegrative change in the deepest layers of the cerebral cortex at the junction with the subcortical white matter. There is degeneration of the ground substance at the depth of the cortex, of such severity that on sectioning the brain it is difficult to prevent cleavage of cortex from subcortex. This amounts to a pathologic undercutting of the cortical gray matter. Production of periodic electrical bursts in these cases may well represent a natural experiment comparable to laboratory studies of isolation of the cerebral cortex, by means of which similar EEG patterns of burst activity with silent intervals have been experimentally produced.

Discussion:

DR. PAUL F. A. HOEFER (New York, N.Y.): I was quite interested in this paper. I have a group of 12 cases all of whom have periodic bursts in the EEG and all of whom have shown, at least at times, a rather severe diffuse encephalopathy rather than encephalitis. Nine of the 12 had generalized seizures; 4 have died; the other 8 recovered without residuals. The clinical entities ranged from inclusion body encephalitis to encephalitis associated with infectious mononucleosis, measles; developed mental anomalies, and myoclonus epilepsy.

DR. LEVIN (*closing*): The main point I would like to make is in agreeing with Dr. Hoefer that this EEG pattern is not diagnostic of a disease as is generally considered in various countries of the world where a diagnosis of subacute encephalitis is made, a clinical diagnosis which is based upon this EEG pattern.

It is our feeling that the EEG pattern represents a physical state and is not diagnostic of a particular clinical entity.

19. Some electroencephalographic findings in patients who experience their first seizures in the post-partum period. — MILTON M. PARKER and ROBERT P. CALHOON, White Cross Hospital and Ohio State University, Columbus, Ohio.

The initial occurrence of seizures in the post-partum period poses a frequent clinical problem. The manifestations vary widely. Most often they entail odd bits of stereotyped behavior which are not recognized as automatisms by those who are not intimately familiar with the epilepsies. We have obtained electroencephalographic tracings from a group of patients who had never experienced any ''spontaneous'' alterations of consciousness prior to the post-partum period. In general, these initial episodes occurred within six months following delivery. The types of seizures ranged from the major clonic-tonic-coma episodes through akinetic grand mals and psychomotor attacks. Some of the pregnancies had been complicated by toxemia of varying degrees. Many had been entirely unremarkable. The role of the latent dysrhythmias, essential and secondary, the effects of the toxemias and the general nature of other provocative processes are discussed in the light of the electroencephalographic findings and the clinical data.

Discussion:

DR. VICTOR M. VICTOROFF (Cleveland, O.): In the absence of any definition of what is meant by ''epilepsy'', I would not say that Dr. Parker's group of patients are all epileptic, but I certainly think that he has pointed up a new approach to the para-partum neuropathic women.

These patients manifest symptoms of severe dissociation with many phobic disturbances and go all the way to severe psychosis.

I would like to ask whether Dr. Parker has considered that perhaps many of his patients may have been para-partum psychotics rather than or in addition to their being epileptics. I should be most appreciative to hear his answer to this.

DR. PARKER (*closing*): Each of these patients had been referred by a physician who had observed at least one of the alterations of consciousness.

I submit that I did not attempt to elaborate *in extensia* what I mean by epilepsy, but feel that that would be gilding the lily here. Some of the alterations of consciousness were rather incomplete; others quite obvious and typical.

None of these patients was psychiatrically remarable. They had usually a simply described complaint which was given directly and with little difficulty; and it was corroborated by at least one relative.

20. Simultaneous psychological and electroencephalographic testing in epileptics. — H. BIRNET HOVEY and KENNETH A. KOOI, Veterans Administration Hospital and University of Utah College of Medicine, Salt Lake City, Utah.

Twenty-one epileptic patients were selected for combined electroencephalographic and psychological

testing on the basis of having demonstrated bursts during previous electroencephalograms. An electronic transform of the questions and responses was recorded with the electroencephalogram in order to investigate possible intercorrelations between the paroxysmal transients, variables associated with the test procedure, and kinds of responses. Control and test runs were obtained both with eyes open and closed. It was found that non-answer responses (NRs), which have been shown in a previous study (*Arch. Neurol. Psychiat.*, 1955, *74*: 287-291) to occur more frequently in epileptic patients than in organic or psychiatric patients, were significantly correlated with burst activity. Requests for repetition of the question and ''don't know'' responses often indicated concurrent bursts. Differences in incidence of bursts occurred between control and test periods, whether eyes were open or closed, and also, between early and late portions of each subtest. Combined testing appears to be a useful method of assessing certain alterations of mental function associated with paroxysmal activity.

Discussion:

DR. WALTER (Los Angeles): We found this paper most interesting and we too have been interested in the problem of the interruption by these paroxysmal bursts of relatively long and ongoing behavior. I think that this technique is a most attractive one. Dr. Yeager and I have been troubled largely with methodology in an attempt to study this phenomenon. It certainly has been a longstanding puzzle in EEG to try and find some way of detecting clinical manifestations of these quite apparent bursts in the tracing.

I might report briefly one method that does not work. We thought that if we made a little device so that the tracing would be audible to the subject than at the time that it was being recorded, then the subject might have some information that an event had occurred.

As you know — I am sure you have all had the experience — you have seen bursts in the tracing and then go in afterwards and ask the patient: ''Did you notice anything in particular during this time ?'' and I suppose with Dr. Kooi's terminology, you would get a zero response: ''Who ? Me ? No, I didn't notice anything.''

We thought if the subject could hear some specific break at the time that it occurred in the EEG, then he might be able to make observations and describe to us some subjective phenomena that he had experienced.

We observed the same phenomenon that Dr. Kooi has already deported.

The number of bursts during the time the patient listens to his own EEG is difficult to produce and I suppose this is a result of the lurking phenomenon, the increased vigilance on the part of the patient. However, occasionally the burst comes through. There is a quite clearly audible signal. I am sure the patient must hear it. Then we question the patient at some length and then frequently we get the zero response even to such an extent as: ''Huh ? Who ? Me ?''.

21. Distortion in the "usual" seizure pattern induced by anticonvulsant medication: A clinico-electroencephalographic study. — NICHOLAS A. BERCEL, University of Southern California Medical School, Los Angeles, California.

Observations have been for a long time on record about the modifications in the ''usual'' seizure pattern of epileptics while under therapeutic trial. Most references emphasize three orders of changes: (*a*) persistence of aura and ''ghost'' seizures before complete seizure control is established, (*b*) the first occurrence of one type of seizure facilitated by certain drugs fully effective for another type, and (*c*) emergence of psychotic states when the seizures (mostly psychomotor) are under control with temporary remission of the psychosis when seizures recur. Considerably less information is available about the EEG changes which monitor such departures from the ''usual'' seizure pattern.

Over the course of thirteen years serial EEG's were done in these cases and data were collected in an attempt to correlate such factors as etiology, age of occurrence of seizures, combination of seizure types, serial EEG changes and the drugs employed. The distortion of the ''usual'' seizure pattern affords some insight into both the spreading mechanism and the pharmacological action of anticonvulsant drugs. It would appear that the greater precision in the recognition of minor seizures and the greater number of combinations possible with the plethora of drugs on the market in recent years contributed to a rise in pattern distortion during the therapeutic trial.

22. The electroencephalogram in narcolepsy. — DAVID DALY and ROBERT E. YOSS, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

Narcolepsy, although a common disease, has received little attention from electroencephalographers. Previous reports are both few and contradictory, some authors emphasizing a high incidence of abnormal records. Other authors have attempted to relate the disease to the convulsive disorders. In view of this, further study of the problem seems justified.

The present paper is based on studies of 100 patients with narcolepsy. As might be expected, drowsiness is a frequent complication during the recording, and often makes it difficult for the patients to reach a true basal state. In this series, when a true basal state could be obtained, the majority of the records were within normal limits and followed a distribution which would be anticipated for members of the general population without neurologic disease.

Unlike non-narcoleptic persons, the patients are likely to remain for long periods in the so-called floating stage or state of semidrowsiness. Procedures which in normal patients would induce arousal — for example, counting or eye-opening — are insufficient to arouse narcoleptic patients fully. Such patients may, therefore, remain in a twilight state, neither alert nor asleep, for protracted periods. The electroencephalogram during this time shows changes similar to those described by Davis and associates in their studies on normal persons during drowsiness. The records are unusual only in that this stage persists, rather than passing over into either sleep or arousal. Since this state may be present from the onset of recording, errors in interpretation caused by failure to recognize this feature may commonly result. ''Paradoxical alpha-blocking'' may be seen; when this occurs, eye-opening induces sufficient arousal to evoke the alpha rhythm, while eye-closing is followed almost immediately by drowsiness with disappearance of the alpha rhythm. In the drowsy state certain automatic actions may be carried out without the

patient's being fully aroused; for example, hyperventilation may continue in such a patient during the drowsy state, giving the illusion that the patient is entirely awake.

Recordings made during cataplectic attacks in one patient and during sleep paralysis in another patient showed no abnormalities.

Discussion:

Dr. Strauss (New York): The results of the authors correspond essentially with my own and are in contrast to some confusing reports on abnormalities of the EEG in narcolepsy. All I have found in narcoleptics are patterns of drowsiness and sleep. In contrast to the authors, however, I have not only found superficial but also deep sleep. This is possibly due to the fact that I take the records with the patient lying down, while the authors recorded with the patient in a sitting position. I obtained one record in a patient with sleep paralysis during which the record showed a normal waking pattern.

Dr. Daly (*closing*): Actually, in a number of these patients when we tried to get sleep recordings, we had no difficulty. And you are quite right, that the reason they didn't go to sleep in our recordings is due to the circumstances under which we recorded them, plus the fact that we were trying to keep them awake so that we could get an alert record.

I am aware of Roth's paper and I think that this is only a coincidental occurrence. In our series of 241 patients we had only one patient who had a convulsive disorder, so I think that this, too, we must consider coincidental.

23. The Metrazol activated electroencephalogram in normal subjects. — Robert N. Baker and Donald W. Klass, 3700th USAF Hospital, Lackland Air Force Base, Texas.

The electroencephalographic changes associated with the intravenous injection of Metrazol (pentylenetetrazol) were studied in 50 normal subjects. This study was undertaken in order to provide a ''control'' series with which to compare the Metrazol activated electroencephalogram when used as a diagnostic tool. The initial paroxysmal change in the electroencephalogram evoked by Metrazol, the ''threshold response'', has been used by some to differentiate between ''normal'' and ''abnormal'' subjects. Our experience and a review of the literature led us to question this concept.

Fifty young Air Force men between the ages of 17 and 28 were selected from a random population after being screened to exclude all who had a history of head injury, syncope, headaches, seizures or other neurological conditions. These subjects were given a complete medical and neurological examination, psychological testing and appropriate laboratory studies in order to exclude any significant disorder. A routine electroencephalogram including hyperventilation and photic stimulation was performed on each subject prior to Metrazol administration. A 5 per cent solution of Metrazol was administered by continuous intravenous injection at the rate of 50 mg. per min. until the appearance of a diffuse, paroxysmal, atypical spike-wave discharge, or until 1000 mg. of Metrazol had been given.

Thirty of the first 32 subjects studied showed a diffuse, atypical spike-wave discharge at an average of 510 mg. of Metrazol, with levels ranging from 190 to 900 mg. These levels were distributed evenly, throughout the entire range. In two subjects given the full 1000 mg. of Metrazol, no such discharges were evoked. The various types of EEG changes are described in detail. No focal changes were observed.

When the amount of Metrazol injected is limited to 350 or 500 mg., the electroencephalographic response of many normal people will be excluded. The differences in ''threshold'' averages among previously reported series of ''normals'' using similar techniques may be largely accounted for by such arbitrary limits. The so-called Metrazol ''threshold'' varies over such a wide range in normal subjects that it seems unwarranted to set an arbitrary level to distinguish ''normal'' from ''abnormal''.

24. The mechanism of diphasic skin potential response. — Chester W. Darrow, Robert C. Wilcott, Ann Siegel, Jere Wilson, Kyozo Watanabe and Richard Vieth, Institute For Juvenile Research, Chicago, Illinois.

It was shown by Forbes and Bolles that diphasic skin potential following more intense conditions of stimulation might arise from a single skin area rather than being a result of opposed differently timed reactions under the respective electrodes. This has been recently confirmed by Wilcott, *et al.*, in this laboratory, both by recording against established inactive skin areas and by simultaneous records triangulating three electrode areas. To account for simple negative deflections under moderate excitation and for negative followed by positive deflections on more severe arousal we obtained simultaneous continuous records of actual sweat secretion by an earlier described technique. It is shown that diphasic patterns occur in association with stimuli sufficient to bring moisture to the surface of the skin. The general level of sweat activity rather than the severity of stimulation is shown to be the determining factor.

When the sweating response is insufficient to fill the sweat ducts the galvanic electrode picks up electrical changes in tissue surrounding the sweat tubules, whereas with filling of the sweat ducts electrode contact of maximum conductivity is with the interior of the sweat gland. This accounts for the initial negative followed by delayed positive deflections. The change form monophasic to diphasic skin potential pattern when recording from a single active area may thus provide useful information on level of excitation correlating with EEG or other bodily changes.

25. The use of chlorpromazine for sleep tracings and for the control of restless or excited children and adult patients. — Martin L. Towler, University of Texas, Galveston, Texas.

The value of sleep tracings as well as the time consuming difficulties coincident to obtaining satisfactory sleep recordings is well known. The difficulties coincident to electroencephalographic examination of infants, children and excited, psychotic and delirious patients is common experience. In our experience, chlorpromazine given by intra-muscular injection about twenty minutes prior to time of examination is a safe and very effective means of quieting difficult patients and inducing sleep from which patients can be readily aroused.

THE EASTERN ASSOCIATION OF ELECTROENCEPHALOGRAPHERS

The Hartford Hospital, Hartford, Conn.

September 30, 1956

Secretary: Dr. JOHN W. SCOTT
Toronto General Hospital, Toronto, Ont., Canada

1. The effects of bufotenine on the EEG. — Wm. J. Turner, Sidney Merlis, Anthony Correoso and Lawrence Grolnick, Central Islip State Hospital, Central Islip, N. Y.

Intravenous injection of bufotenine into schizophrenic subjects produced only slight slowing and drop of alpha amplitude, when the rate of injection was in the order of 0.34 mg. per kilo per hour. The rapid injection of 0.2 mg. per kilo of bufotenine led to profound disturbance of consciousness, hyperpnoea followed by apnoea, intense flushing of the face, chest and hands, and salivation. Immediately following the onset of hyperpnoea slowing of the EEG occurred, the rate dropping to 0.5 - 2 per sec. Even after 0.4 mg. per kilo, recovery occurred in 10 to 15 min., with no evidence of aggravation of the psychosis or appearance of hallucinations. Barbiturate spindles were abolished and replaced by slow activity. Premedication with chlorpromazine led to profound drops in blood pressure. One subject, pre-medicated with reserpine and Pentothal had a dangerously prolonged apnoea with 0.04 mg. per kilo of bufotenine.

2. The worth of serial electroencephalograms. — J. A. Churchill and S. Gonzalez, Division of Neurology and Division of Neurosurgery, Henry Ford Hospital, Detroit, Mich.

In the practice of EEG, one of the most critical questions asked by the clinician is whether his patient has an intracranial tumor or a cerebro-vascular accident. A single EEG yields findings that are quite similar in both conditions, there being few or uncertain clues to the identity of the lesion.

Taking into consideration the different dynamic course of events, how reliably can those who have tumors be distinguished from those who have CVA's with two or more EEG's ? Records of 26 patients with brain tumors and 63 patients with CVA's were studied. Initial EEG's were rated positive, borderline, and negative. Progress EEG's were compared with their antecedents and were rated worse, unchanged, and improved. The 26 cases presented diagnostic difficulties, the original diagnosis of tumor being made in only 4 cases. The original EEG was positive in 15 cases, borderline in 6, and negative in 5. In the group of CVA's the original EEG was positive in 56, borderline in 3, and negative in 4.

All but 4 of the tumor cases had progress EEG's that were worse than the first. Three cases remained unchanged. The progress EEG in one case was slightly improved, no reasonable explanation being found for the apparent improvement. About two-thirds of the CVA group had progress EEG's which were improved. Six cases were worse than the original EEG, 3 of them clearly revealing that they had had new CVA's. Of the other 3, the progress EEG was taken within 3 weeks of the time of the icti. Progress EEG's in 12 cases remained unchanged. In 6 of them, the original record was obtained one to two months after their icti had occurred.

The number of cases presented is small but nevertheless it was possible to calculate standard errors of per cent at a level of significance of three standard errors. It was found that in the usual group of tumors presented for progress EEG's at least 83 per cent would show worsening of the EEG signs and in any other group of patients with CVA's, 74 per cent or more of them would show improvement in the EEG.

It is concluded that a fairly high degree of accuracy can be achieved in the separation of patients who have tumors from those with cerebro-vascular accidents by the use of serial EEG's. It is recommended that when the question whether the patient has tumor or cerebro-vascular accident is not solved quickly progress EEG's should be obtained. The first one in two weeks, the next one in one month, and others at chosen intervals.

3. Abnormal electroencephalograms in a penal setting. — Eugene Revitch, Menlo Park, N. J.

In the light of reports on abnormal EEGs in children with behavior disorders, in the so-called psychopathic personalities and in the prison population, 15 aggressive female inmates of the New Jersey Reformatory for Women and one male inmate of Annandale Reformatory were studied at length psychiatrically, neurologically and electroencephalographically. All of them were late adolescents and young adults. Their personality make-up was characterized by suspicious, paranoid orientation. Their behavior was marked by severe outbursts of temper with assaultiveness, destructiveness, pseudo-suicidal acts and alterations of consciousness. Only one of the 16 patients is known to have had seizures under influence of alcohol. The psychogenic nature of alterations of consciousness in others was demonstrated through a two year follow-up. Twelve patients had perfectly normal EEGs with well developed alpha activity. The 4 abnormal records were as follows:

1. Delta bursts and 20 per sec. fast activity.
2. S_1 record.
3. Bursts of delta activity in the posterior leads.
4. Focal delta bursts in right hemisphere.

Only the patient with # 1 abnormal record had alterations of consciousness originally suspected as being of epileptic origin, while the patients with similar alterations had normal records. It is believed that the 4 abnormal EEGs are only incidental to the abnormal behavior.

4. Mesencephalic and hypothalamic influence on seizure duration (in the cat). — O. Andy, R. McC. Chinn, P. Springer, S. Gillis and P. Bonn, Laboratory of Experimental Behavior, Division of Neurosurgery, University of Mississippi Medical Center.

In a series of 25 freely moving cats, seizures were serially induced in the cingulate gyrus and the hippocampal system structures. After-discharges were induced by electrical stimulation (over 800 trials) every 2 to 4 min. Each series of stimulations was divided into 2 to 4 blocks containing 10 or 21 stimuli. Within alternate blocks, each stimulation was preceded by an electrical stimulus applied to mesencephalic, diencephalic or other limbic system structures. After histologically verifying points of stimulation and recording, the behavioral and electrical changes were correlated and the electroencephalographic seizure durations were serially plotted for each experiment.

Stimuli applied to the ventral tegmental area of the mesencephalon and posterior hypothalamus would invariably be accompanied by overt activation of the animal. The electrical response was typical of the cortical and subcortical activation patterns previously described. During the repeated cingulate gyrus induced seizures the animal invariably would sleep. However during the series of cingulate gyrus seizures which were preceded by mesencephalic or hypothalamic stimulation, the cat would remain awake throughout the entire series. This type of behavioral change appeared to be associated with a curtailment of the over-all seizure duration.

In a few experiments this behavioral change was not evident but the electrical activation pattern was definitely present and correlated with the altered seizure duration. As much as 70 per cent reduction of the seizure duration was associated with hypothalamic or mesencephalic stimulation. An illustrative experiment is No. 27 which had a series of 84 serial stimulations divided into 4 blocks of 21. Each of the cingulate after-discharges in the first block was preceded by posterior hypothalamic stimulation and the total seizure duration for this block was 146 sec. Hypothalamic stimulation was omitted in the second block and the total cingulate gyrus seizure duration increased 28 per cent (188 sec.). Hypothalamic stimulation was reintroduced in the 3rd block and the seizure duration decreased 75 per cent (48 sec.). In the 4th block the hypothalamic stimulation was again omitted and the total seizure duration increased 59 per cent (117 sec.) over the previous block.

In general the effect of stimulating the hypothalamus and mesencephalon on hippocampal system seizures follow a similar pattern.

5. Correlation analysis of depth recordings from the basal ganglia. — Mary A. B. Brazier and John S. Barlow, Mass. General Hospital and Mass. Institute of Technology, Boston.

We have been fortunate in being given the opportunity by Dr. William Sweet to record the EEG from areas in the basal ganglia of patients with Parkinson's disease prior to the making of therapeutic lesions. In one case we were able, in addition, to make tape recordings for later analysis by correlation. The settings for the stereotactic insertion of the electrode needle were determined by Dr. Sweet and Dr. Kjeleberg from X-rays with pantopaque. The electrode was a multiple one with 7 recording points along its shaft. The conducting material was copper, the wires being insulated from each other. Through a burr-hole on the right, the electrode shaft was inserted parallel to the interaural line. In addition to the depth recording points scalp and muscle electrodes were used. All electroencephalograms were recorded both on an inkwriting oscillograph and on a 5-channel frequency modulated magnetic tape-recorder. The latter recordings were then examined by correlation analysis for the following phenomena: intrinsic periodicity; interdependence of structures in regard to their electrical properties; and time relations of such relationships if found.

The rhythms of the intrinsic activities of these basal ganglia appeared to be independent of each other and of the cortical rhythms. They were also independent of the periodicity of the muscle tremor. All rhythms recorded from the brain were of higher frequency than that of the tremor. Crosscorrelations between the various deep structures showed all points in the medial globus pallidus to be simultaneous with each other, but activity in this structure led that in the lateral globus pallidus by 7.5 msec. and that in the putamen by 5 msec. The crosscorrelations between the cortex and the deep structures showed that the former fired first. No correlation was found between the rhythm of the forearm tremor and activity of the cortex or of the deep structures. None of the relationships described above were discernible in the inkwritten trace and emerged only on correlation.

We would like to thank Dr. William Sweet for the opportunity to make these recordings and to acknowledge the collaboration of Dr. R. Kjeleberg, Dr. E. Gasteiger and Mr. F. Eastman in this work.

6. Corneal-retinal potentials in clinical neurological practise. — Robert Cohn, Bethesda, Md.

The corneo-retinal potential may be modeled as a polarized sphere; with the cornea positive and the retina negatively charged. With a fixed electrode placement, the amplitudes of the direct current potentials determined the eyeball position in a two-dimensional framework. The amplitudes of the recorded potentials diminish as the electrodes are displaced from either canthus.

DC recordings of extra-ocular muscular action were made under conditions of normal and impaired function. The latter were obtained from several cases of eye muscle disturbance resulting from various etiologies. By the use of DC recordings one is able to precisely determine the extent of involvement (initial), and the subsequent rates of recovery, of the function of the prime movers of the eyeballs.

7. The EEG in intracerebral hematoma. — Daniel Silverman and Robert A. Groff, Departments of Neurology and Neurosurgery, Graduate School of Medicine, Graduate Hospital, University of Pennsylvania, Philadelphia, Pa.

Intracerebral hematoma, an encapsulated hemorrhage within the substance of the hemispheres, produced a clinical syndrome which often was difficult to differentiate from other vascular insults, tumors, abscesses or at times chronic convulsive states. Ten cases, 9 verified at operation, were studied with the EEG. The most common EEG pattern (7 cases) was of the focal slow wave type, usually in the delta

frequency range, the pattern frequently associated with expanding lesions or massive vascular thromboses. Of these 7, 6 had acutely progressive symptomatology and 4 of these had symptoms or signs suggesting increased intracranial pressure; the 7 had a history of ''strokes'' dating back 3 years prior to the current acute episode, which was accompanied by papilledema. Two patients had focal sharp waves and focal spike-waves, together with slowing in their EEG's; they suffered with chronic convulsive states and only developed focal symptomatology shortly before exploration. The tenth case, who had an acute syndrome and who died without benefit of surgery or autopsy, showed unilateral suppression together with focal slowing. In all patients on whom sleep state recordings were obtained, there was persistence of the delta focus and distortion of sleep potentials with the slow wave focus type, and accentuation of spike activity with the spike-wave type. This was in accord with previous studies on the significance of delta focus changes from waking to sleep state recordings. Patients who were followed with serial studies prior to operation showed increasing abnormality in their EEG's.

8. An EEG artifact resulting from dental restorations. — Rhoda Feinstein Milnarich, Garfield Tourney and Peter G. S. Beckett, Psychophysiological Laboratories, Lafayette Clinic, Detroit, Mich.

A brief description of an artifact closely resembling spike activity is presented. The patient had two fixed bridges in his mouth, one on the lower right, the other on the upper left. The bridges were of dissimilar metals and set up a battery, the discharges of which were recorded on the electroencephalogram and resembled spike discharges.

9. Effect of Equanil on the EEG. — Charles Henry, Walter Obrist, Phyllis Porter and Rosa Anglas, Hartford, Conn.

Meprobamate (Equanil, Miltown) is a long acting derivative of mephenesin without autonomic effects. On oral administration it has a tranquilizing, muscle relaxant and anticonvulsant effect. It is thought to have its site of action in internuncial circuits with emphasis on thalamus. In clinical doses it is alleged to have no effect on the EEG, although animal studies have shown an increase in voltage and decrease in frequency, with a marked synchronization of thalamic activity.

We have repeatedly observed substantial amounts of rhythmic and well defined fast activity in the EEGs of psychiatric patients receiving a wide range of clinical dosage. A total of 79 cases were recorded, 46 of whom were entirely free of other contaminating drugs that might induce fast activity (barbiturates, doriden, chloral hydrate). Excess fast activity was seen in 74 per cent of these records. The effect was most pronounced in patients receiving more than 1600 mg. daily. Seven of 8 cases given 2.0 g. by mouth in a single dose showed subsequent rhythmic 20-30/sec. fast activity maximal anteriorly, beginning as early as 15 min. following ingestion. Two patients given 400 and 800 mg. i.m. showed a slight increase in fast activity.

10. The concept of centrencephalic epilepsy and the spike and wave EEG. — Gilbert H. Glaser, Yale University School of Medicine, New Haven, Conn.

Centrencephalic epilepsy was originally characterized as a minor (petit mal and myoclonic) and/or major (grand mal) seizure state associated with electroencephalographic discharges of 3 c/sec. spike-wave complexes in bilateral synchrony. It was postulated, from experimental evidence, that these seizures originate from the diffuse thalamic projection system. Usually, no definite etiologic factors were found and this group represented the ''idiopathic'' seizures of older classifications.

This concept requires expansion clinically since other, more varied types of seizures have been found to be associated with the typical centrencephalic 3 c/sec. spike-wave discharge. These especially include psycho-motor, sensory, and autonomic automatisms, often with local manifestations. Illustrative cases are presented with clinical and EEG correlations.

Transition from atypical petit mal seizures with a speech component, to grand mal, within a three month period, with correlated EEG changes, is shown in an unusual case of pseudotumor cerebri. As the seizures changed, diffuse delta waves appeared in addition to the 3 c/sec. spike-wave complexes. Both the clinical and EEG abnormalities were relieved by decompression.

There have been increasing suggestions that the 3 c/sec. spike-wave discharges of centrencephalic seizures may actually originate in some instances by unilateral cortical foci discharging centrifugally into a possibly abnormally facilitated diffuse thalamocortical projection system. This mechanism would account for the association of focal automatisms with this type of EEG. A diffuse process, such as increased intracranial pressure, also might activate a predisposed system. We have concluded that the useful concept of centrencephalic epilepsy is best served, therefore, by maintaining the clinical integrity of seizure states on a specific descriptive basis, and by regarding the associated 3 c/sec. spike-wave discharge as essentially non-specific.

11. Dissociation between electroencephalographic and peripheral convulsive discharge. — Hans Strauss, New York.

Presentation of a patient with a 22 year history of focal seizures in his left hand and arm, very rarely becoming generalized. The seizures are often elicited by excessive use of the left hand. The EEG shows numerous focal spikes at the vertex and in the right central region. Most of the spikes are not associated with any peripheral phenomena. Others occur simultaneously with clonic contraction as recorded by the electromyogram. However, clonus also occurs without simultaneous abnormality in the EEG. This dissociation suggests that one is not dealing with a cortical but with a sub-cortical focus which fires as well to the cortex as to the periphery, but not always simultaneously. The similarity of this observation with some recent experimental work by Walker and his co-workers will be discussed.

12. Observations on evoked dendritic activity of human cortex. — D. P. Purpura, J. L. Pool, J. Ransohoff and M. J. Fruman, Department of Neurological Surgery and Department of Anesthesia, College of Physicians and Surgeons, Columbia University, New York.

Although evidence is rapidly accumulating relating to the physiology of apical dendrites in animals no information is as yet available on the nature of human dendritic activity. The present report summarizes initial investigations on this subject with special emphasis on the alterations induced by various pharmacological agents.

Four patients were selected for study, 2 undergoing psychosurgery and 2 exploration for suspected neoplasm. Anesthesia was delivered by means of a CO_2-servo-controlled respirator delivering various nitrous oxide-oxygen mixtures. Paralysis was induced by succinylcholine infusion. Following routine craniotomy surface electrodes were arranged for oscilloscopic registration of evoked potentials. No attempts were made to record from pathological cortex in the tumor patients. Instead a site was chosen for stimulation and recording from grossly ''normal'' cortex. In 3 of the cases penetration of a small cortical artery supplying the sites under observation was accomplished utilizing a # 31 gauge needle attached to a polyethelene cannula in order to deliver pharmacological agents locally.

The 15-20 msec. synaptic potential of apical dendrites evoked from the human cortex was recordable up to 6 mm. from the stimulating site following a weak stimulus when patients were maintained on 70 per cent nitrous-oxygen mixtures. By timing the onset of the negative potential under pairs of recording electrodes with known interelectrode separation a conduction velocity of 0.6 m/sec. has been determined for the pre-synaptic fibers in the molecular layers having synaptic contact with the vertically oriented dendritic elements.

Summation of dendritic activity occurs in paired stimuli only within 10 msec. In all cases, however, the test response to the second stimulus within this period was less than the response when unconditioned. This depression persisted up to 80 msec. after the conditioning stimulus. That the absence of a facilitatory phase during the initial response as observed in the lightly anesthetized cat (Clare and Bishop) was probably not attributable to the nitrous oxide anesthesia employed is demonstrated by the fact that only minimal alterations in dendritic excitability were observed when the patients were permitted to equilibrate on 100 per cent oxygen for 10 min.

Pharmacological studies utilizing the intra-arterial injection method described above with saline controls indicate that unlike cat, human dendritic synapses exhibit a high degree of resistance to d-tubocurarine similar to the monkey (unpublished observations). The response to intra-arterial LSD was similar to that reported in the cat (Purpura), axo-dendritic inhibition developing in the human cortex with an augmented synaptic delay.

13. The anatomical pathways of discharge from one temporal lobe to the other. A preliminary report. — R. Poblete and R. J. Ruben, Baltimore, Md.

These studies attempt to demonstrate some pathways mediating conduction of temporal lobe activity to structures within the contra-lateral hemisphere, in particular the temporal lobe.

Surgical lesions directed to the anterior commissure, corpus callosum and fornix, were made in 7 monkeys. Cortical and subcortical electrodes were used for recording and electrical stimulation (thyratron discharge).

The data suggest that the anterior commissure, septal-fornix region and hypothalamus are some of the anatomical pathways mediating the spread of the afterdischarge from the temporal cortex, amygdala and hippocampus from one side to the other.

14. Electronic frequency analysis of aged psychiatric patients. — W. D. Obrist and C. E. Henry, Institute of Living, Hartford, Conn.

Tape recorded EEGs were obtained on 64 psychiatric patients ranging from 65 to 95 years of age. These were subjected to an electronic analysis by a modified Offner frequency analyzer. The results indicate that it is possible to differentiate groups of aged patients classified according to psychiatric diagnosis and prognosis. Patients with organic mental symptoms (chronic brain syndrome) had significantly slower EEGs than those without evident mental deterioration, as revealed by their frequency spectra. A comparison will be made between the electronic analysis of these cases and a manual frequency analysis obtained on a group of 50 similar patients.

15. A review of Russian Neurophysiology for the past five years. — W. T. Liberson, Northampton, Mass.

ANNOUNCEMENT

MEETING

Western Society of Electroencephalography

February 28-March 1, 1957

LaPlaya Hotel

Carmel, California

CENTRAL ASSOCIATION OF ELECTROENCEPHALOGRAPHERS

St. Louis, Missouri

October 27, 1956

Secretary-Treasurer: Dr. T. J. CASE
950 East 59th Street, Chicago 37, Illinois

1. Stability of photic driving and relation to resting EEG. — LAVERNE C. JOHNSON and GEORGE A. ULETT, Washington University School of Medicine Department of Psychiatry and Neurology and the Research Laboratories of Malcolm Bliss Psychiatric Hospital.

EEG examinations, including resting, and response to an episcotister photic stimulator, were recorded and electronically analyzed on 182 graduate students. To study relationship of photic driving to resting activity, 120 of the initial records were selected for analysis. Data on stability comprise 3 records taken 3 months apart on 50 subjects. Photic driving is defined as the amount of cortical activity present during photic stimulation minus the spontaneous activity during a resting period. Changes both in amount of photic driving and in the shape of driving profile over each of 24 frequencies (3-33 c/sec.) were investigated in the study of stability. Significant differences in amount of driving were found. For this sample, amount of driving is an unstable measure varying from trial to trial. Analysis of stability of driving profile revealed marked individual differences. Some subjects were stable, others very unstable. Range of intra class correlation coefficients was from minus .23 to plus .86 with median of .49. No relationship between photic driving, and resting activity was found. When the resting activity was not subtracted from activity during photic stimulation a positive relationship was obtained.

2. Scalp electroencephalograms of psychiatric patients under treatment with benactyzine (Suavitil). — DWIGHT M. PALMER, Ohio State University, College of Medicine.

Benactyzine (Suavitil) is the hydrochloride of benzilic acid diethylaminoethylester. It has a peculiar blocking action centrally, relieving anxiety by divorcing reality from emotional reactions. It is said to have an effect on the alpha rhythms.

Nineteen patients in a mental hospital were given benactyzine orally over a twelve week period, in doses of 1 to 15 mg., three times a day. Scalp EEG's were recorded before medication, again when the patient was on small doses such as 3 mg. three times a day, and finally after the dosage had been increased to 15 mg. three times a day.

The patient's alpha rhythms were essentially unchanged, by this medication, when subjected to visual analysis. The variations observed were interpreted as those related to changes in the vigilance and somatic tension of the patients.

It would appear that this drug has slight if any direct effect on the alpha activity of the scalp EEG when the latter is subjected to visual analysis.

3. Suggestive and misleading EEG diagnosis in one hundred posterior fossa lesions. — B. K. BAGCHI, University of Michigan.

Misleading cerebral localization was given preoperatively in eight cases, using EEG criteria for depth diagnosis first elaborated in 1952 (*EEG Journal, 4*: 23-40). Depth diagnosis was correct in about 75. Adequate recording time (60-90 min.), scalp coverage, and electrode arrays (and not simply anteroposterior parasagittal bipolar) are paramount in many cases (*Electrochemistry in Biology and Medicine*, John Wiley and Sons, **1955**, 331-351). In absence of epilepsy, "degenerative", acute traumatic or inflammatory condition previously described types and degrees of bursts are suggestive of a deep lesion including one in posterior fossa. Correct contralateralization of lateralized tumors with or without associated vermian, fourth ventricular or pontine involvement and having contralateral EEG dominance (contralateral statistical emphasis of bursts and not necessarily amplitude dominance as literature has mistakenly interpreted us) was 77 per cent. Considering 100 lesions, including purely midline ones, correct contralateralization was 55 per cent. Third ventricular and chiasmatic tumors are often difficult to distinguish from posterior fossa lesions.

4. Clinical and EEG responses to single pulse depth stimulation in epileptic patients. — R. G. BICKFORD, H. MCDONALD, H. W. DODGE and A. UIHLEIN, The Mayo Clinics, Rochester, Minnesota.

5. Sleep EEGs in psychiatric patients. — JEAN M. NICHOLSON and JOHN R. KNOTT, Division of EEG, Department of Psychiatry, State University of Iowa College of Medicine.

Sleep recording was obtained in routine EEGs of 162 unselected psychiatric in-patients. Similar recording was obtained in 218 patients referred with a possible diagnosis of convulsive disorder, and 59 patients with other neurological disorders. The average ages of these groups were: 34, 28 and 35 yrs., respectively. The youngest patient in each group was 12 yrs. of age; a relatively greater proportion of cases between 12 and 20 yrs. occurred in the convulsive group.

Temporal sharp or spike activity was seen in 10 per cent of the psychiatric group, 11 per cent of the convulsive disorder suspect group, and in 10 per cent of the "other neurological disorder" group. The 14 and/or 6 per sec. positive spike pattern was seen in 20 per cent of psychiatric patients, in only 6 per cent of convulsive disorder suspects, and 9 per cent of "other neurological disorders".

The psychiatric group was broadly subdivided into those with: (1) *chronic brain disorders* (23); (2) *psychotic disorders* (46); (3) *non-psychotic, non-organic disorders* (93). The incidence of temporal sharp or spike activity was: 22, 11, and 7 per cent, respectively. The incidence of other sharp activity was: 4, 11 and 3 per cent, respectively. Fourteen

and/or 6 per sec. positive spike activity appeared in: 0, 15 and 28 per cent, respectively.

The high incidence of the 14 and/or 6 per sec. positive spike pattern in the psychiatric group (especially the non-organic, non-psychotic patients, variously diagnosed as: (*a*) psychophysiologic autonomic and visceral disorders; (*b*) psychoneurotic disorders; (*c*) personality disorders; and (*d*) transient situational personality disorders) would seem to warrant further exploration with particular reference to: (1) symptomatology related to the pattern; (2) etiological relationships of symptoms and EEG; (3) efficient avenues of therapeutic approach to psychiatric patients presenting 14 and 6 per sec. positive spikes in their EEGs.

6. Generalized increased electrical activity as an evidence of tumors. — THEODORE J. CASE, EEG Laboratory, University of Chicago Clinics, Chicago, Illinois.

Many people with tumors show increased electrical activity in the EEG which is equally distributed over the cerebrum. Although much of this contains delta waves and some of these delta waves are localized, there is a surprising number in whom there are no delta waves and no localization is possible.

Most of these patients are children or adolescents and their increased activity is often indistinguishable from that which is seen in children with convulsive diathesis. Are these people with an inherent convulsive diathesis which has been in some way exaggerated by the tumor, or has the tumor caused an increase of electrical activity in some other fashion ?

There is another group in which adults predominate whose activity has a large component of frequencies at 10 per sec. or faster but usually irregular. Although it sometimes suggests a convulsive diathesis, this suggestion is usually not so clear as in the first group.

The tumors causing these changes may be anywhere in the brain. They are perhaps most frequently in the midline cerebrum but may be subtentorial; or perhaps even in the upper cord.

7. Some effects of chlorpromazine on subcortical electrical activity. — R. E. CORRELL and W. W. KAELBER, Departments of Anatomy, Psychiatry and Neurology, State University of Iowa.

Effects of chlorpromazine on subcortical electrical activity were investigated in cats. Four to 5 bipolar electrodes were implanted for chronic studies in areas of the diencephalon, rhinencephalon, basal ganglia and reticular system. After allowing for operative recovery, chlorpromazine (7-21 mg/kg.) was injected intramuscularly and continuous EEG recording was done for an average of 2 to 4 hours. Records were compared with those of alertness, light natural sleep and Serpasil. Photic stimulation was carried out before and after drug administration.

Generalized slowing and voltage increase occurred in all structures investigated to a varying degree. These changes correlated with time from administration and amount of drug. Behavioral effects could not be explained solely in terms of the generalized slow activity, but may relate to certain specific effects, such as a demonstrable residual mild slow in the region of the thalamic reticular nucleus. Chlorpromazine had little effect on photic driving.

8. Pharmacologic activation in clinical study of convulsive disorder. — DOUGLAS GOLDMAN.

Technique for the use of intravenous Pentothal in very small doses for producing activation of convulsive patterns and localized abnormalities in the electroencephalogram is described with illustrative material from case studies. Normal control subjects are compared with convulsive disorder, showing the extent of responses in normals as compared with the clear activation which takes place in convulsive disorder even when the tracing in the convulsive patients in the resting state is entirely normal. This is of diagnostic importance in an appreciable number of patients.

9. Electrical activity of the spinal cord of the salamander and its modification by seizures and by severance of spinal nerves. — JOSEPH J. PETERS, ALPHONSE R. VONDERAHE and THOMAS H. POWERS, Cincinnati, Ohio (Illustrated by motion pictures).

During recordings of electrical activity from unanesthetized salamanders 8 electrodes were placed so as to span the brain, and the pectoral, lumbar, and pelvic regions of the spinal cord. In salamanders curarized to a depth of immobility, a convulsive dose of Metrazol is followed by spike-like electrical activity which at times may be fundamentally the same in frequency and amplitude along the length of the spinal cord, or this electrical activity may show local fluctuations without corresponding changes in the brain or in adjacent areas. A severance of spinal nerves at the pectoral region modifies electrical activity at this area during seizure phenomena. Salamanders with spinal nerves cut at the pectoral region still present the basic swimming pattern described by G. E. Coghill in his behavioral studies.

10. Superimposed oscillographic traces as a qualitative method to determine inter-channel phase and other differences in EEG. — B. K. BAGCHI, University of Michigan.

This is a preliminary report. Dawson has used a superimposed trace technique to study evoked response from the scalp following peripheral stimulation. Here two different traces of the record of normals or abnormals are superimposed to detect phase, voltage and wave-length differences between homologous areas, anterior versus posterior areas, latero-medial linkages versus antero-posterior parasagittal linkages. With X selector off and using common sweep two spots of a dual beam cathode ray oscilloscope can be superimposed one on the other and equivalent voltage calibration ascertained. EEG signals are fed into two beams through appropriate preamplifiers. Then 5 to 20 seconds of fast motion picture of the EEG is taken, one beam made slightly lighter than the other for later identification on sensitized paper. Some interesting differences are noted. The efficacy of the method, however, needs further evaluation.

11. Additional studies on cerebellar influences on the reticular activating system. — JOHN BLUNDELL and RAY S. SNIDER, Department of Anatomy, Northwestern University Medical School, Chicago.

The present study is an outgrowth of previous studies by Henneman *et al.* (1950); Cooke and Snider (1953). In both papers there was established a

cerebellar influence on cerebral activity. The present paper reports on possible intermediate mechanisms which may be involved.

Single electrical pulses were applied to discrete cerebellar areas and recording electrodes were placed in various nuclei of the diencephalon. The nuclei reticularis and centrum medianum of Luys gave consistent responses with latencies as short as 6 msec. for the first of three peaks which were usually recorded. Since these nuclei are part of the so-called reticular activating system, we interpret these data to indicate that the cerebellum can exert an influence on this system. Experiments are in progress to determine more precisely what some of these influences are.

All experiments were carried out on cats under ether and d-tubocurarine anesthesia.

12. The use of Noludar in pediatric electroencephalography — Don L. Winfield and James G. Hughes, Departments of Neurology and Psychiatry, and Pediatrics, University of Tennessee, College of Medicine, Memphis, Tennessee.

This report is concerned with the use of Noludar for inducing sleep in pediatric electroencephalography. Noludar is a newly developed hypnotic, distinguished by high therapeutic activity and low toxicity. In view of the reportedly quick action of Noludar, the elixir form was administered routinely and the results obtained from a study of 278 consecutive EEGs on children between the ages of 2 months and 15 years are reported. Noludar produced sleep in a reasonable length of time and did not generally induce fast activity in the record. It appeared to be particularly effective with behavior problem referrals and with those children who are generally excited by the barbiturates. No undesirable side effects were noted during the study although no systematic attempt was made to investigate them.

13. Electroencephalography in the brain injured child. Studies in sedation. — V. Richard Zarling, Minneapolis, Minnesota.

In the course of recording electroencephalograms on children with mental deficiency and with various types of brain damage, various medications have been evaluated for use in relaxing the patient sufficiently to permit an adequate study to be made. Approximately 100 children of various ages have been studied using morphine or a combination of hyascine, morphine and cacodylate. The results have indicated that sleep is easily produced in the patient and they remain quiet in spite of using either bentonite or needle electrodes, — that sleep occurs spontaneously and arousal is possible. Electroencephalographic abnormalities present are not altered on this medication. In a few instances, uncomfortable but not severe side reactions were experienced and these are described with accompanying electroencephalograms.

The use of the HMC combination, provides a safe and practical medication for obtaining electroencephalograms on the restless, hyperactive, or apprehensive brain injured child.

14. Changes in water content and electrical activity of the cerebrum following acute closed cerebral injury. — P. Cooke, R. A. Clasen, F. Martin, J. R. Williams and G. M. Hass.

Circumscribed lesions of the cerebral cortex were made through an intact calvarium in a series of adult dogs using an instrument which permits local freezing with liquid nitrogen. After thawing, the portion damaged, grossly resembles a contusion or a hemorrhagic infarct. Microscopically, adjacent white matter is edematous and stained by intravenous injection of Evan's blue solution, as is the lesion. Measurements indicate increase in water content of the damaged hemisphere, which correlates directly with extent of damage, but not with amount of hemorrhage. Electroencephalograms taken during and after freezing show permanent inactivation of the area frozen. In other regions, patterns become simpler, amplitude and frequency decrease; changes resembling those accompanying asphyxia or Nembutal anesthesia. Alteration, always greater on the side damaged, may progress after thawing. Following a variable recovery period, secondary deterioration begins. Its earlier onset may be due to hemorrhage, but after three hours it is associated with significant increase in water content.

15. Distant evoked responses to depth stimulation in patients with neurologic disease. — Reginald G. Bickford, Hugh N. A. MacDonald, Henry W. Dodge, Jr. and Collin S. MacCarty, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

These observations were made among five nonpsychotic patients in whom depth leads had been implanted as a preliminary to surgical excision for focal seizures. Gradual refinement in our technique of stimulation has made it possible to record from most depth contacts during stimulation. Stimulus isolation with slow repetition (1 per sec.) and short pulses (0.3 msec.) is employed. It has been found, first, that many different kinds of response patterns can be evoked at a considerable distance (transhemispheric and occipitofrontal) from the stimulated area. These include spikes, sharp waves and complex rhythmic waves lasting up to 2 sec. and with amplitudes up to 2,000 μV. Second, an increase in stimulus voltage results in an increase in amplitude, complexity and duration of the response. Third, in some instances the background rhythms are triggered, and in other cases large responses may appear from a flat background. The same contacts may show different response patterns when these are evoked from different stimulus loci. Fourth, responses are modified during sleep, and are much reduced and simplified under barbiturate anesthesia. Fifth, with some exceptions, the responses are subclinical and unnoticed by the patient. They usually occur equally well during sleep, and do not arouse the patient.

The findings indicate the existence of a system the stimulation of which by a single pulse evokes widespread and dramatic disturbances in the resting rhythms. Maps can be constructed to give functional interconnections which may be important in (1) localization (functional) of the stimulus locus, (2) study of transmission problems in the brain, (3) quantitating of the action of anticonvulsant drugs, and (4) study of the initial processes of the self-sustained seizure discharge.

16. Periorbital D-C and A-C measurement of eye potentials relating voltage changes associated with variations in eye position to repeatable fixation shifts made in response to controlled stimulus position changes. — Christine Kris, University of Chicago, Chicago, Illinois.

THE EEG SOCIETY

ADDENDUM TO THE EUROPEAN MEETING: SYMPOSIA ON DRUGS AND ON RECORDING, INSTRUMENTATION AND PROCESSING OF DATA [1]

London, England. May 24-26, 1956

1. Polygraphies des modifications de la conscience. — H. Fischgold et P. Mathis, (Paris).

Les corrélations entre l'EEG, la respiration et le rythme cardiaque dans le sommeil, le coma et le petit mal ont été publiées au colloque de Marseille.

Les auteurs exposent cette fois-ci quelques recherches sur le réflexe psycho-galvanique, le temps de réaction et la traction rythmée.

Réflexe psycho-galvanique.

Se laisse inscrire à l'état de veille, de sommeil, à l'occasion de paroxysmes de petit-mal; paroxysmes cliniques ou infra-cliniques, spontanés ou provoqués; les auteurs ont constaté sa présence même dans un cas d'inconscience prolongée accompagné de silence électrique complet du cortex.

Temps de réaction.

Son intérêt dans le sommeil est minime: car le top trop sonore réveille le sujet qui a souvent oublié la consigne et ne répond pas, tout en étant conscient.

Dans le paroxysme de petit-mal, on connait sa valeur depuis Schwab; les auteurs insistent sur le délai de la réponse en rapport avec l'amplitude de la pointe et de l'intervalle qui sépare le top de la pointe.

Traction rythmée.

Proposée pour le petit-mal par Shimazono, la traction rythmée constitue d'après les auteurs la meilleure technique d'étude de l'endormissement. La traction rythmée n'empêche pas le sujet de s'assoupir, cesse au moment d'une très courte bouffée de somnolence dès que le rythme alpha s'aplatit et reprend en même temps que l'activité alpha, dès que le sujet remonte vers un niveau plus élevé de conscience.

L'arrêt de la traction rythmée peut être interprété dans certaines situations comme un oubli de la consigne; le temps de réaction reprend alors ses avantages.

Car la traction rythmée tire son intérêt de sa simplicité: exécution régulière d'une consigne. Simplicité qui l'oppose au temps de réaction: réponse à un signal; réponse absente ou présente, rapide ou retardée, exacte ou fausse.

Ces tests du "niveau" de la conscience ne sont discutés que du point de vue de la technique et des indications respectives. Chacune mérite une application systématique en voie de réalisation dans le Centre d'EEG de l'Hôpital Pitié (Paris).

2. The action of chlorpromazine on the EEG of infants. — R. Laplane, R. Humbert, P. Laget and R. Salbreux, (Laboratoire de Physiologie des Fonctions, Université de Paris).

A study has been made of the effects of chlorpromazine (Largactil) on the EEG of 30 children less than 2½ years old who were clinically normal and had EEG's which were definitely within the normal range.

In 14 subjects the drug was administered orally in doses of 2 to 5 mg. per kg. of body weight; in the other 16 it was injected intramuscularly in doses of 1.5 mg. per kg. In the first group, the treatment was continued for several days in order to achieve adequate saturation; when the intramuscular route was employed, the recordings were made one hour and a half after the injection.

In most cases (about 50 per cent) chlorpromazine produced no change in the electrical activity either in the waking or sleeping state. In the very young babies (less than 3 months) the voltage of the physiological rhythms seemed to be definitely reduced. Finally for the remainder of the children, particularly those receiving intramuscular injections, there was some slowing of the basic rhythms and an overall augmentation of amplitude.

It would seem that in these latter cases it was not a matter so much of the direct action of the drug on the cortical electrical activity, as the progressive induction of physiological sleep being reflected in the EEG changes. Moreover when the action of the drug was so pronounced as to induce sleep, this showed all the features of normal slumber, as much from the characters of the reaction to visual, tactile and painful stimuli as from the appearance of the EEG.

In conclusion, chlorpromazine seems to be particularly useful for the induction of physiological sleep in very young children. Apart from the practical convenience which could be provided by its routine use in obtaining satisfactory records from babies, it can help in the study of the onset of drowsiness. It has enabled the authors to work out in very young children the relations and changes of electrical activity during the transition from wakefulness to sleep; this work is still in progress.

3. Review of radio EEG development. — C. S. Parker, C. Breakell and F. Christopherson, (Whittingham Hospital, Nr. Preston, Lancs.).

About 1948 the idea of transmitting EEG by radio between fixed points was successfully concluded by us, using a crystal controlled frequency modulated transmitter in which the special difficulties of this mode were overcome.

Identical, directly recorded and radio transmitted EEGs were obtained over a distance of half a mile. (*Lancet*, 1949, i, 167.)

Very shortly after this we conceived the idea of ambulant EEG and attempted our first portable EEG transmitter. The first really successful model was amplitude modulated by a sub carrier which carried the EEG in the form of frequency modulation. (*Lancet*, June 27, 1953, p. 1285). This permitted the subject to move freely about whilst simultaneously his EEG was radio transmitted and recorded at a suitable receiving point (apparatus A).

This apparatus was, however, much more bulky than we wished and our next step was to miniaturise the apparatus as much as possible. To this end a form was produced with a frequency modulated sub carrier (apparatus B). This was further improved into apparatus C (see photographs).

This still kept our ambulant subject tied to a distance limited by the range of the portable apparatus from a fixed point (200 yards). Conse-

1 *EEG Clin. Neurophysiol.*, **1956**. *8*: 699-724.

quently a further step was taken by producing a portable receiver with its own pen and paper drive (apparatus D). This greatly enhanced the mobility of the subject and by following him in a car carrying the portable receiver we were able to allow him almost unrestricted liberty of movement by combined mobility of the receiver and range of portable EEG transmitter.

At this stage a further step became possible with the introduction of miniature wire recorders of extremely light weight and small size. We utilised the Minifon portable wire recorder and were able to combine our portable EEG with the miniature wire recorder to obtain a completely mobile EEG unit. This made a less complicated apparatus suitable for those purposes where direct sight of the recording was not needed immediately (apparatus E).

This left us with two forms of portable EEG which could be worn by the subject as he moved about:

(*a*) A radio operated version where simultaneous observation of the record was required.

(*b*) A wire recorded version which could be interpreted later.

EASTERN ASSOCIATION OF ELECTROENCEPHALOGRAPHERS

New York, December 5, 1956

Secretary: J. W. SCOTT

Toronto General Hospital, Toronto, Ont., Canada

1. Evaluation of "organic" features in childhood schizophrenia. — PHILIP S. BERGMAN, SOL NICHTERN and CHARLOTTE WEISS, Bellevue Medical Center, New York.

Childhood schizophrenia is a clinical entity meaning different things to different people. According to Bender and her associates, the muscular and neurological performance of some of these patients and their responses on certain psychological tests suggest organic dysfunction of the brain. These characteristics are held to indicate defective maturation of the nervous system and are essential to her concept of this disease. Abnormality in the EEG, if present, would give additional evidence in support of this viewpoint. Unfortunately, previous EEG studies of childhood schizophrenia have been equivocal. The EEG's of schizophrenic children are generally within normal limits, and normality is certainly the rule in adults with schizophrenia.

In the present study, consecutive cases of childhood schizophrenia were divided into two groups: (1) those with pronounced "organic" features in psychological and selected neurological tests, and (2) those with little or no evidence of "organicity". The behavior of these patients, both in the hospital and in the home, was essentially the same in the two groups. Cases of frank neurological disease, including epilepsy, as well as those who had had electroshock therapy or significant amounts of drugs, were not included.

EEG's were done awake and asleep. They were all interpreted by one of the investigators (PSB), who did not know the clinical status at the time of the reading. The clinical data were supplied by a series of psychological tests, extended observations of behavior, and other studies, which will be described.

The results suggest possible avenues for further investigation of childhood schizophrenia.

2. Epileptogenic effects of implantation of various metals in the cerebral cortex of monkeys. — JOSEPH G. CHUSID, LENORE M. KOPELOFF and NICHOLAS KOPELOFF, St. Vincent's Hospital, New York.

Twenty-six different metals were implanted in the precentral motor cortex of 38 monkeys (Macaca mulatta). Pure metals were used and in most cases implantations were made bilaterally. This group of animals has now been observed for periods ranging from 6 to 12 months; all but 6 monkeys still survive so that this study is presented as a progress report. Since an attempt was made to screen a wide variety of metals, in many cases a single animal was prepared with a particular metal. Studies included clinical observations, serial electroencephalograms and testing of convulsive response to vigorous prodding, intramuscular Metrazol (24 mg/kg.) and intravenous Picrotoxin (0.4 mg/kg.). The pure metals surveyed included: lead, silver, chromium, cobalt, manganese, tantalum, zinc, tin, magnesium, aluminum, silicon, zirconium, gold, iron, molybdenum, tungsten, beryllium, thallium, copper, mercury, antimony, bismuth, nickel, tin, cadmium and vanadium. Clinical convulsions occurred spontaneously or could be induced at some time by vigorous prodding, intramuscular Metrazol or intravenous Picrotoxin in monkeys with cerebral implantations of antimony, bismuth, vanadium, zirconium, copper, titanium mercury, nickel, cadmium. The clinical convulsive reactivity was most persistent and pronounced in the case of antimony. Severe toxic fatal reactions were noted in the animals with bilateral thallium, nickel, mercury, cadmium, and beryllium. Electroencephalographic changes when present were most pronounced in the early postoperative phases (4-12 weeks), at which time diffuse slow dysrhythmias, sometimes associated with spike or sharp wave patterns, occurred.

3. Abdominal epilepsy; A case report. — JOSEPH L. O'BRIEN and ELI GOLDENSOHN, Department of Neurology, Neurological Institute, Columbia-Presbyterian Medical Center, New York.

Paroxysmal abdominal pain as a form of epilepsy is a fairly well established clinical entity. Several series of patients have been reported in which both the clinical and the electroencephalographic findings have been detailed. In only one of these cases, however, was an EEG recorded during an actual attack of pain. This report deals with the second instance in which modification of the EEG occurred with an episode of paroxysmal abdominal pain. The patient is a 9 year old girl who has had recurrent episodes

of peri-umbilical pain since the age of 5. These occurred at 5 to 6 week intervals and lasted about 5 days each. During the course of her study two EEGs were taken between bouts of pain. These were interpreted as mildly abnormal because of some suggestive paroxysmal features. A third tracing was obtained during an attack. This consisted of partly synchronous high voltage 3 c/sec. waves in all leads. Another EEG obtained two days later when the pain had disappeared but when the child was still subdue and withdrawn showed occasional bursts of 3 c/sec. high voltage waves with large amounts of 4-6 c/sec. activity. A follow-up EEG taken one month later was considered essentially the same as the other interim tracings. Etiologic factors and possible mechanisms of abdominal seizures are discussed.

4. Further analysis of inhibitory activity in the cerebral cortex. — Dominick P. Purpura, Edgar M. Housepian and Harry Grundfest, Departments of Neurological Surgery and Neurology, College of Physicians and Surgeons, Columbia University, New York.

A series of previous studies have indicated that excitatory and inhibitory synaptic electrogenesis comprises the electrical activity recorded from the surface of the brain. Inhibitory action is relatively weak in the cerebellar cortex which accounts for the ability of reticular stimulation to drive synchronous, rapid activity in the cerebellum. In contrast, the effects in the cerebral cortex of the same stimulus are predominantly inhibitory for the surface negative dendritic potentials.

A more detailed analysis of reticulo-cortical effects is the subject of the present report. High frequency reticular stimulation eliminates the surface negative dendritic component evoked in the cerebral cortex by antidromic pyramidal volleys. The inhibitory action also extends to the response of the pyramidal tract to direct cortical shocks.

Single stimuli delivered to the mesencephalic portion of the ascending reticular system evoke cerebral cortical responses of different configuration in different cortical areas. When, as occurs in the anterior suprasylvian gyrus, the negative component predominates a conditioning activity may abolish or reverse the negativity in a testing response delivered as long as 500 msec. later. The predominant positivity which is evoked in the anterior sigmoid gyrus is unaffected or augmented at the same time. Responses evoked by direct cortical stimuli condition subsequent activity of single reticular volleys in the same way. In those cortical regions where the latter evoke negative responses the testing activity is abolished after a previous cortical stimulus. Where positivity is produced, the testing response is augmented.

Cortical or subcortical ''refractoriness'' is not involved since repetitive reticular stimulation at 10-25/sec. may partially overcome these effects. Long persisting excitatory actions by single reticular stimuli are disclosed by the augmentation of the direct cortical response following a prior reticular conditioning volley.

Differences in the relative proportion of inhibitory and excitatory electrogenesis evoked in different cortical areas, both by reticular stimuli and by the direct appear to account for the results described above.

5. Paroxysmal electrical silence in the sleep EEG of infants. — Robert Jaffe and Suzanne Lewyn, Mount Sinai Hospital, New York.

Intermittent periods of gross flattening of the tracing appeared as an abnormality in 8 of 8000 consecutive routine EEGs. The abnormal records were all sleep tracings in infants less than 2 years of age, natural sleep in one case, barbiturate-induced in the others.

The abnormality (paroxysmal electrical silence) was sometimes seen only in one lead, or only on one side; sometimes shifted from side to side, but was usually bisynchronous. In some cases the intervening activity consisted of spikes and sharp-waves, in others of slow-wave bursts, in others of normal sleep activity.

The clinical and pathologic pictures were varied, but there were some common features. Six of the 8 patients had seizures, and all had evidence of severe diffuse organic brain disease.

The possible mechanism underlying the abnormalities seen in our patients will be discussed, as will the relationship of these findings to the ''suppression-burst'' activity of Henry, and the ''isolation-phenomenon'' of Echlin.

6. Electrical studies in experimental myopathy. — Gilbert H. Glaser and Lawrence Stark, Yale University School of Medicine, New Haven, Conn.

Muscular excitability as measured by refractory period was determined in young rabbits with metabolic myopathy induced by cortisone (14 rabbits treated for 4 to 40 days) and potassium-free diet (6 rabbits for 16 to 58 days). Control observations were made in 10 normal animals. Quinidine was administered to 9 rabbits to evaluate the method with known drug effects. Needle electrodes in the paravertebral muscles were used for both stimulation and recording. Shape and duration of muscle action potentials evoked by maximal stimulation were studied oscilloscopically. Recovery of excitability was plotted in terms of responsiveness to a second stimulus.

The control absolute refractory period was of the order of 0.8 msec. and did not alter significantly in the experimental states. The relative refractory period, with a time constant circa 1.6 msec., was not changed in cortisone myopathy, despite severe muscle degeneration. This indicated preservation of enough normally responsive fibers. Both potassium-deficiency and quinidine induced a prolongation of this time constant to over 2.8 msec.

7. An experimental analysis of a neural oscillation. — Lawrence Stark and Tom N. Cornsweet, Yale University School of Medicine, New Haven, Conn.

Many explanations have been put forward suggesting possible mechanisms for the wide variety of oscillations seen in the electroencephalogram and in clinical neurology. Oscillations are also a common and important instance of malfunctioning of servomechanisms. It seems reasonable to attempt to interpret and understand this phenomenon in similar terms for both engineering and biological systems.

The pupil reflex to light, an example of a neurological servosystem, was studied using servoanalytic concepts and techniques. The graphic analysis and

transfer function demonstrated system behavior to be stable and non-oscillatory because of low loop gain. Conversely, it could be predicted that if gain were increased (for example, by manipulating stimulus light distribution), then the system should oscillate at the phase-crossover frequency (in this case 1.2 c/sec.). This prediction was verified.

Clearly, in this situation, neural components of the reflex are in oscillation. We propose that this neural oscillation be considered as a model for other (but, of course, not all) neural oscillations. Its advantages as a model are: (1) it consists of a well-defined anatomical and physiological entity; (2) it operates as a relatively simple servomechanism; (3) its system parameters have been experimentally measured, and (4) its analysis has been verified by a successful prediction.

8. Pharmacologic activation of the electroencephalogram in convulsive disorder. — DOUGLAS GOLDMAN, Cincinnati, Ohio.

Activation of the electroencephalogram is often desirable to add to the diagnostic usefulness of the procedure. Use of Pentothal intravenously for bringing to light pathologic activity which otherwise would not be apparent in the record, has been the subject of study for the last year, and the results are described in this preliminary report. An important contribution to this method has been published in August, 1956, in the Journal of Electroencephalography and Clinical Neurophysiology, by Schneider and Thomalske, who described the use of Pentothal in recognition and localization of neurosurgical lesions.

Our material consisted of patients with convulsive disorder, for the most part severe and chronic, and normal non-convulsive controls. A resting electroencephalogram was made in routine fashion prior to injection of Pentothal, then 2 or 3 doses of 0.1 gram (or 0.05 gram in children or very small individuals) were injected rapidly intravenously at intervals of 2 to 6 min., so that a cycle of effect could be observed in its entirety with each injection. The effect of Pentothal activity was in many respects similar to the activation produced by normal (non-drug induced) sleep, but represented a much more sharply controlled observation particularly for depth of sleep. In addition, certain observations probably represent specific Pentothal effect.

The results may be summarized as follows:

(1) In patients in whom the resting tracing is obviously pathologic, Pentothal activation may show increase in pathologic activity or may produce more sharply localized abnormality.

(2) Patients in whom the resting tracing shows no pathologic activity, injection of Pentothal brings to light pathologic changes which in some instances are similar to those produced by sleep, but which are more reliably produced by the use of Pentothal with the technique described.

(3) Patients in whom there is gross organic cortical dysfunction show different, probably more intense and significant change following Pentothal. This is of probable theoretic importance and requires further study.

9. Electroencephalographic and neurological changes associated with 6-azauracil administration. — C. E. WELLS and C. AJMONE-MARSAN, National Institutes of Health, Bethesda, Md.

6-Azauracil, a new experimental anti-tumor agent, has been given to 19 patients. In 17, it has induced significant electroencephalographic and neurologic changes. EEG changes have consisted of: abolition of the fast rhythms; disorganization of the background activity with moderate amplitude, irregular slowing; depression or disappearance of the response to photic stimulation; and appearance of high amplitude delta rhythm, diffuse bilateral and very often rhythmical at 2/sec. Clinically, the most striking change has been lethargy progressing to subcoma. The discrepancy between the electrographic changes and the clinical abnormalities has been striking, the electrographic abnormalities generally appearing considerably before any clinically detectable change. All manifestations induced by the 6-Azauracil have regressed when the drug was discontinued. The changes induced were directly related to the dosage of the drug employed. Children appeared more susceptible than adults to its toxic manifestations. Its mode and site of action are unknown.

10. Ionization and the EEG; A preliminary report. — DANIEL SILVERMAN and IGO H. KORNBLUEH, Departments of Neurology and Physical Medicine, Graduate School of Medicine, Graduate Hospital, University of Pennsylvania, Philadelphia, Pa.

Ionization of the air, a normal component of our atmosphere, can be changed radically by the production of ions through a radioactive ion generator or other methods. Since it was known that such artificial ionization caused certain general and local physiologic reactions, its effect on the human EEG was studied. Ten neurologically normal and two neurologically damaged subjects were given electroencephalographic examinations before and during negative and positive ionizations. A consistent finding was a decrease in the occipital alpha rate of ½ to 1½ c/sec. during the early stages of either ionization, which occurred in 10 of the 12 subjects. This decrement was seen in 3 with positive, 4 with negative and 3 with both ionizations. It reached a maximum from 12 to 18 minutes after the initiation of ionization and then diminished. Concomitantly most subjects experienced some dryness of the upper respiratory apparatus and mouth, relaxation and sleepiness. The implication of these findings are briefly discussed. It is suggested that ionization may exert a transient ''tranquilizing'' effect on the brain and that further research is warranted by this preliminary experiment.

11. EEG and clinical response to Megimide. — MARTIN A. GREEN and MAX FINK, Research Service, Hillside Hospital, Glen Oaks, New York.

Megimide (NP 13, ethylmethylglutaric acid imide) was administered to 40 psychiatric patients either before or after the administration of intravenous amobarbital sodium. Intravenous Megimide induced diffuse paroxysmal slow wave, spike, and spike-wave activity in the electroencephalogram and myoclonic twitches clinically. In one instance a grand mal seizure was induced. The degree of the abnormality was related to the rate and amount of drug administered. The amount necessary to induce abnormality varied from 4 to 50 cc., at rates of administration of 4 to 10 cc. per min. No specific sequence of induced abnormality was observed.

Intravenous amobarbital after Megimide considerably reduced the amplitude and per-cent time of the paroxysmal activity. Although the barbiturate was given in quantities sufficient to induce clinical signs of barbiturate intoxication, the beta activity in the EEG was minimal or absent.

In patients premedicated with intravenous amobarbital in amounts necessary to produce nystagmus, slurred speech, and drowsiness, Megimide often alerted the patient with a disappearance of these clinical signs of barbiturate action. However, the beta activity induced by barbiturate persisted.

Megimide appears to be similar to Metrazol in its EEG and clinical effects. In addition, Megimide may have specific anti-barbiturate activity.

12. Electrical stimulation of cingulate gyrus (Behavioral study) [1]. — ORLANDO J. ANDY, RALPH MCC. CHINN and PHILIP BONN, Laboratory of Experimental Behavior, Division of Neurosurgery, University of Mississippi Medical Center.

It has been previously proposed that an epileptogenic focus originating in the cingulate gyrus cortex may induce a convulsive diathesis, by way of the cingulum, throughout the hippocampal system.

In this study an attempt was thus made to correlate the electroencephalographic and behavioral changes occurring during a seizure induced by electrically stimulating the anterior and posterior limbic cortex (primarily in its supercallosal portion).

Twenty-five freely moving unanesthetized cats were employed for this study. Subcortical triple stainless steel Hess electrodes were inserted to various subcortical structures and screw electrodes to the dura overlying specific cortical areas. The scalp was injected with ½ per cent Novocaine to facilitate the insertion of electrodes. Histological localization for all points of recording and stimulation has been done on all brains.

Results. Electric discharges from the cingulate gyrus are characterized by a relatively slow frequency, simulating the patterns obtained from the cortical area. In contrast to hippocampal seizures, cingulate gyrus seizures are extremely short in duration, lasting 5 to 10 sec. The cingulate gyrus seizure will spread to the hippocampal system only if suprathreshold stimuli are employed. Behaviorally, the cat has a marked tendency to sleep during a cingulate gyrus after discharge. If the discharge spreads to other cortical and subcortical structures, the cat will awaken and become activated. Stimulation of the anterior cingulate area in several animals has produced a very striking pupillary constriction. This is in marked contrast to other limbic structures which, if any change, will produce a pupillary dilatation.

1 Aided in part by a Grant (B-815) from National Institutes of Health, U. S. Public Health Service.

THE EEG SOCIETY

Maudsley Hospital, London, England

October 5, 1956

Chairman: Dr. D. A. POND
Secretary: Dr. S. SHERWOOD
Institute of Medical Research, Mill Hill, London, N. W. 7

In addition to the papers of which summaries are given below, the following discussions took place at the meeting:

''A transistor-operated EEG with D.C. amplification''. A demonstration and description of the apparatus with special reference to its use in the study of eye movements. Dr. F. Offner (Chicago).

A discussion on the interpretation and diagnosis of EEG records.

Dr. P. B. Bradley (Birmingham) gave a brief report of the Symposium on Brain Stem Reticular Formation held in Brussels earlier in the year.

1. Autonomy of alpha rhythm generators studied by multiple channel cross-correlation. — E. G. WALSH (Department of Physiology, Edinburgh University).

Adrian and Yamagiwa (1935) believed that the alpha rhythm was produced by two generators — one in each parieto-occipital region. They thought that the activity of the two sides was synchronised — ''their phase relation cannot vary''. In contrast Eccles' (1953) theory of the alpha rhythm would predict independence. Essential to a discussion of these viewpoints is knowledge of polarity relationships along a line of electrodes disposed transversely across the back of the head. The literature on this point is confusing. Adrian and Yamagiwa found one phase reversal on each side and occasionally one at the midline also but Beevers (1944) who alone appears to have attempted verification could find one focus only — sometimes on one side, sometimes on the other.

Graphic methods alone were available to Adrian and to Beevers and these are scarcely equal to the complexity of the problem. The question has been re-examined by the use of an instrument that automatically detects polarity relationships computing all six paired combinations of four channels. The behaviour of the device to complex waveforms has been considered and is satisfactory. When desired the system may be rendered frequency sensitive by the use of resonant chokes.

In normal adults there is usually evidence of two phase reversals, but at times one of these may vanish. Activity from regions on either side of the two phase reversals either (1) does not cross-correlate; or (2) is in antiphase.

This finding gives clear evidence of the existence of independent generators. The picture that emerges is of two autonomous sources beating at about the same rate. Confusion with graphic techniques would be expected in such a situation, for the polarity rela-

tionships at any instant will depend upon the phasing of the two sources and this will vary in a random fashion.

References:

ADRIAN, E. D. and YAMAGIWA, K. *Brain*, **1935**, *58*, 323.

BEEVERS, C. A. *Proc. Roy. Soc. Edin.*, **1944**, *62*, 43.

ECCLES, J. C. "The Neurophysiological Basis of Mind." **1953**.

2. An improved electrotoposcope. — H. W. SHIPTON (Burden Neurological Institute, Bristol).

The frequency and phase indicating toposcope is limited in its application by the chosen method of integration. In normal use photographic exposures of about 1.5 sec. are made and in studies of the potentials evoked by repetitive photic stimulation a speed of 4 r/sec. is typical. There are thus 6 sweeps over which responses are summed. As the amplitude of artefacts or unwanted spontaneous signals can exceed 6 times the mean signal level an ambiguity results.

There are two further limitations to the original method:

1. The storage medium (film) is monotonic.
2. The brightening circuits lead to a reduction in the maximum obtainable resolution.

To overcome these limitations a system has been devised in which a spiral scan is used. The diameter of the scan is increased smoothly during the camera exposure so that repetitive signals lie on the same angular bearing but with changing radius. Thus trace-to-trace correlation is substituted for the summation process of the earlier system. It has been shown that this leads to an improvement in signal noise ratio, moreover, the ambiguities referred to above no longer arise.

The application of this method to the study of evoked potentials is described and some results are given and compared with those obtained by more conventional techniques.

References:

SHIPTON, H. W. A toposcopic display system using a helical scan. *Proc. EPTA.* (In Press).

TUCKER, D. G. and GRIFFITHS, J. W. R. Detection of pulse signals in noise. *Wireless Engineer*, **1953**, *30*: 264.

WALTER, W. G. and SHIPTON, H. W. A toposcopic display system applied to neurophysiology. *J. Brit. IRE*, **1951**, *2*: 260-284.

WALTER, W. G. and SHIPTON, H. W. A new toposcopic display system. *EEG Clin. Neurophysiol.*, **1951**, *3*: 281-292.

3. The effect of chlorpromazine and reserpine on sedation and convulsive thresholds in schizophrenic patients. — P. M. JEAVONS and P. B. BRADLEY (The Medical School, Birmingham).

In view of the suggestion that chlorpromazine potentiates the action of barbiturates and antagonises convulsants, it was thought worth while to study the effects of this drug, together with another tranquillising drug, reserpine, on convulsant (hexazol) and sedative (sodium amytal) thresholds in man, in an attempt to obtain a quantitative estimate of their action. This has been done in a group of twelve chronic schizophrenic patients.

The method used for establishing the sedation threshold was a modification of that of Shagass (1954). The method adopted for determining the convulsive thresholds was modified from that of Ulett *et al.* (1955). Both thresholds were determined in all patients before any pre-medication, and then after chlorpromazine and reserpine.

The results obtained showed that neither chlorpromazine nor reserpine produced any appreciable change in the convulsive threshold. The effects of pre-medication with reserpine on the amytal threshold was slight, and only the combination of chlorpromazine (pre-medication) and amytal showed any significant change. Here four subjects showed a definite fall in threshold and in one there was a slight fall, although five others showed no change and in one there was a slight rise.

The results and their significance in relation to the methods used will be discussed, together with the value of such methods for assessing drug effects in man.

References:

SHAGASS, C. *EEG Clin. Neurophysiol.*, **1954**, *6*, 221-233.

ULETT, G. A., BROCKMAN, J. C., GLESER, G. and JOHNSON, A. *EEG Clin. Neurophysiol.*, **1955**, *7*: 597-607.

ERRATA

August 1956 issue of the *EEG Journal*

Page 399, 1st paragraph. Discussion, 11th line should read "deep barbiturate anaesthesia"; page 400, last line "The time scale is... etc. should be a footnote to 1st sentence of last paragraph.

November, 1956

Page 550, second column, line 7 "30 min." should be changed to "60 min."; line 16, "40 min." changed to "70 min."; page 555, second column, line 17, "15° C" should be changed to "22° C".

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BOOK REVIEW

Edited by CHARLES E. HENRY

BRAIN MECHANISMS AND CONSCIOUSNESS

Edited by E. D. ADRIAN, F. BREMER and H. H. JASPER

Charles C. Thomas, Springfield, 1954, 556 pp. $8.50

A belated review such as this one does serve a purpose. Time for digestion has been allowed, the voracity induced by the interesting subject matter is abated and one's critical faculties are therefore less impaired. The question asked by the reviewer at this time is not, ''shall I recommend this book to be read ?'', but, ''shall I recommend that it become a part of the reader's reference library ?''. With respect to *Brain Mechanisms and Consciousness,* an unreserved ''yes'' is the answer.

The reviewer has successfully used this reference as recommended class-room reading for courses in physiology and neuropsychology. Magoun's concise chapter makes easily available some of the important findings of his laboratory group. This chapter can be amplified by readings from the chapters by Moruzzi and Olszewski. A similar organization of the reading material concerning diencephalic mechanisms starts with Jasper's superb chapter which contains much that is new and challenging from a theoretical standpoint and must be given adequate time and discussion for proper assimilation. The sections of this chapter which deal with axodendritic and axosomatic synapses and with laminar microelectrode analyses are well on their way to being classics in the literature. These sections are amplified by readings from the chapters by Grey Walter and Brazier. Jasper's statements regarding anatomy are somewhat more controversial and are best juxtaposed to the chapter by Nauta and Whitlock. As yet unresolved differences appear — differences which arise from the different techniques which are used to analyze the problem. But these differences are the very soil in which subsequent experiment flourishes — and unless the student (and teacher) has the differences in mind, new data will fail to excite his interest.

A third series of chapters which makes the symposium a sourcebook of data relates observations subsequent to cerebral stimulation on conscious man. Penfield's chapter, and Richard Jung's, amplified by readings of some of the sections of Gastaut's chapter serve usefully to indicate a frontier of science where data are as yet difficult to evaluate — though they are of great interest.

The remaining chapters are centered around various behavioral processes: sleep, perception, thought and consciousness. There is much in these chapters to warrant reading and reading — but for ideas rather than for data. Not that these chapters are devoid of data, but the data, even when they are neural, are picked and chosen to accord with the behavioral frame of reference. These chapters by Adrian, Hess, Fessard, Hebb, Lashley, Kubie and Rioch show daring and ingenuity — and reflect our abysmal ignorance concerning the very problems that called the symposium. The discussions, which form one of the most readable portions of the book, also support this feeling. Often an attempt is made to mold the paucity of neural mechanisms to the richness of experience; sometimes the one — sometimes the other is ignored. Rarely is a precise statement of a behavioral process linked by discrete experiment to a precise statement of neural mechanism. But the attempts which are made are valiant ones — and those of us who are interested in continuing the effort find as much worth in the ideas expressed (albeit vaguely) in these latter chapters as in the data which form the earlier ones. Conclusion: a superb reference; and many thanks to the editorial staff which has made it available.

KARL H. PRIBRAM

PRINTED IN CANADA

RECEPTORS AND SENSORY PERCEPTION

A discussion of aims, means, and results of electrophysiological research into the process of reception

RAGNAR GRANIT. Yale University Press, 1955, 369 pp., $5.00

A number of the classics in the literature of physiology of this century owe their genesis to the stimulus of the Silliman Memorial Lectureship at Yale University — among them the *Integrative Action of the Nervous System* (Sherrington), *Respiration* (Haldane), *Blood* (L. J. Henderson), and *The Anatomy and Physiology of the Capillaries* (Krogh). Sherrington's lectures that formed the basis for the text of *The Integrative Action of the Nervous System* were delivered in 1904 though the book itself did not appear until two years later. Acclaimed at once as a work of outstanding importance the book served to refashion thinking in neurophysiology for it gave those interested in the field a foundation of experimental observation upon which were erected broad generalizations fashioned with rare philosophic insight into meanings biological. The book provided an immense stimulus to research and largely determined the direction in which the subject was to develop for the three decades that followed its appearance.

The Silliman Committee in their selection of the lecturer for the year 1954 may well have been guided by a desire to recognize in a fitting fashion the golden anniversary of Sherrington's lectureship and its importance for the subsequent development of research and teaching on the physiology of the nervous system. In any event the choice of the lecturer for that year was a happy one and admirably served that worthy purpose for Professor Ragnar Granit, Director of the Nobel Institute for Neurophysiology in Stockholm and an outstanding contributor to the advancement of our understanding of sensory mechanisms was one of Sherrington's pupils. Granit's interests have been centered primarily in two areas of investigation — the electrophysiology of the retina and the role of the sensory system in the regulation of muscular tone; the latter area represents an extension of the fundamental researches of Sherrington on decerebrate rigidity and the function of the intrinsic afferents of skeletal muscle.

These interests form the central themes of the chapters of this monograph — the lectures of 1954 — and their great value stems from the fact that — like Sherrington's lectures fifty years earlier — they are a well documented record of first hand experience in the laboratory. Certainly no one could write with such authority about the physiology of muscle receptors, the reflexes they evoked and their interplay with spinal and supraspinal systems in the regulation of muscle tone, for Granit and his coworkers are in large measure responsible for the elevation of our understanding of ''spasticity'' and ''rigidity'' from what might be designation an ''anatomical'' to a ''physiological'' level. Their disclosure of the role of the motor control to the intrafusal fibers in regulating the firing frequency of the spindle has clarified a host of phenomena among them — the lengthening and shortening reactions and the ''claspknife'' reflex — that were previously without mechanistic explanation. Their demonstration that the ''sensitivity'' of a receptor or group of receptors can be set and rest at a particular level by another group of neurons has not only broadened our concept of the function of sensory endings as physiological meters, it has reawakened interest in the functions of the efferent fibers to the cochlea and retina and given wider significance to the phenomena of ''circus excitation'' first emphasized by Hinsey and Ranson.

How far attention has shifted from the properties of the axon — and the form of the impulse — to those of the terminals of the neurons in the search for the unifying principles of neural activity and interaction is especially evident in Granit's excellent treatment of the primary processes of the sensory receptors. Recognition of the ''slow potential'' as the generator and antecedent of the rhythmic response to the steady state serves not only to bridge the gap between sensation — as quantitated by the Weber-Fechner law — and the stimulus intensity but to point up the fundamental similarity between the properties of sensory and motor neurons — a similarity early emphasized by Adrian and his pupils. The role of the neuron as a conductor and transmitter emerges as secondary to its capacity as a generator and integrator. Even the low safety factor at the site of the expansion of a sensory fiber at the junction of its smaller branches is clothed with an integrative function.

Similarly Granit has given new meaning and importance to the spontaneous activity of sensory endings and centrally placed neurons i.e., retinal elements. The burden of proof is at last placed upon those who would deny the existence of true spontaneous impulse generation. Where it occurs the suggested role of the spontaneous activity of sensory

endings is to energize central systems — to provide a central drive or level of excitation; from this concept, and the evidence in support of it, extend new and fruitful avenues of thought that — tested by experiment — may offer firm bridges to aspects of neurology now the domain of the psychologist. Granit makes especially clear the importance of spontaneous activity in those cases in which the mechanism for excitation is subject to peripheral inhibition i.e., the labyrinth and muscle spindle, against a background of central activity a decrease in the peripheral signal is seen to have meaning as capable of interpretation as a rise.

This is a book that takes its proper place along with the other physiological classics born of the Silliman lectureship.

DONALD H. BARRON

MEDICAL RESEARCH : A MIDCENTURY SURVEY

Vol. I American Medical Research: in Principle and Practice, 765 pages.
Vol. II Unsolved Clinical Problems: in Biological Perspective, 740 pages.

THE AMERICAN FOUNDATION, NEW YORK.

Little, Brown & Company, Boston. $15.00.

A comprehensive intelligible survey of the entire field of medical research in biological perspective would seem an impossible task to anyone actively engaged in any special branch of research or medical practice. After reading these two volumes with growing enthusiasm and sustained interest one must admit that such an impossible task has been achieved with remarkable success, not by a specialist in medical or biological research, but by a non-medical woman, Esther Everett Lape, in charge of a non-medical Foundation whose purpose is ''through fundamental and objective studies to clarify public thinking on subjects on which public thinking was notably nonexistent or confused''. The ''public'' should include, in this case, medical research workers as well as workers in the physical and biological sciences.

Each of the special fields is treated with equal critical competence, and with a sustained theme of the dependence of all medical research upon basic biological research. This extends from our understanding of virus infections or the principles of growth in normal and cancerous cells to our understanding of mental disorder such as schizophrenia.

This work is the culmination of 15 years of study with the aid of a distinguished list of consultants including George Bishop, Ralph Gerard, William Lennox, Francis O. Schmitt and Paul Weiss, familiar names to readers of this Journal.

The first volume deals largely with administrative aspects, organizations and financial support together with basic philosophy underlying the rapid expansion and direction of medical research in the United States. Some idea of the scope of this work is given by the chapter headings:

1. Medical Research in the Perspective of Biological, Chemical, Physical, Mathematical Science, 2. Current Trends and Current Problems in Medical and Biological Research in the United States, 3. Research Agencies, 4. Clearing Results and Controlling Products of Medical Research. This is not a dry account of budgets and institutional organization. It is a searching authoritative analysis of basic principles underlying the most productive organization of medical and biological research and the training of research workers. Emphasis is upon the importance of the basic sciences, physical and chemical, as well as biological, and upon the development of research in University settings rather than in specialized Institutes.

In the second volume will be found more of special interest to readers of this Journal. It begins with a lucid review of ''Current Metabolic Concepts Orienting Research in Biology and Medicine'' including molecular mechanisms, cellular metabolism, correlation of chemical and electrical phenomena of nerve function, and neurohormonal mechanisms of metabolic equilibrium and adaptation. Specific examples are then taken for detailed treatment: *cancer, infertility, arteriosclerosis, hypertension,* the *rheumatic syndromes, tuberculosis,* the *nature of viruses and of virus diseases, alcoholism* (stressing metabolic approaches to an outstanding psychological and social problem) and *biology of schizophrenia* (illustrating interactions of physiological, psychological and social factors).

In summarizing current views regarding chemical and electrical events in nerve tissue the sodium-potassium theory of Hodgkin and Huxley, and Eccles, is compared with the metabolic theory of Lorente de Nó as supported by the work of Bronk and associates. ''Energy rich phosphate is generated in neural tissue by the same mechanisms as in other tissues. This leaves to be answered the question as to the source or trigger mechanism of the specific change in permeability which generates the bioelectric potential for transmission of the nerve impulse along the

fiber and from cell to cell.'' Chemical mediators are then considered briefly.

The chapter on schizophrenia is much more than its name implies. It includes not only a succinct review of this mental disease as a psychiatric and social problem, but a review of most of the leading basic work on the physiology of the brain in relation to behavior, in keeping with the prevailing emphasis upon basic research as most important even in our attempt to understand the most baffling and complex of medical problems such as schizophrenia. ''Those interested in the dimensions of the present research field in schizophrenia would do well to bear in mind that a great deal of the ultimately — and presumably — pertinent neurophysiological work is being done by workers not in the least concerned with mental illness: there are men who have been working on the single axon for years whose interest continues to be — not schizophrenia but axons.''

Magoun is cited as being of the opinion that ''the most valuable contributions to understanding of schizophrenia are likely to come from long-time studies on the neurophysiological correlates of behavior''. Adrian is quoted (1954) that we are at least ''beginning to trace a clearer connection between what is going on in different parts of the brain and what we happen to be doing from moment to moment. For what it is worth, we can see a physical reason for our restless lives and insatiable curiosity''. Recent concepts of cerebral localization of function and the integrative and activating functions of the reticular system are brought to bear on this problem. The importance of metabolic endocrine or toxic factors in schizophrenia is emphasized, though psychoanalytic, social, and cultural factors are presented in fair perspective.

Naturally in such a comprehensive work there must be many omissions, with many important subjects receiving too scant treatment. However, I have never read such a rich and critical condensation of so much important information so well written around a central theme of grand proportions, the importance of basic research in development of scientific understanding of medical value. This is a major achievement. The addition of a style of writing which carries the interest even through the most unfamiliar and difficult ground makes this book a pleasure to read as well as a landmark in biological research of medical importance.

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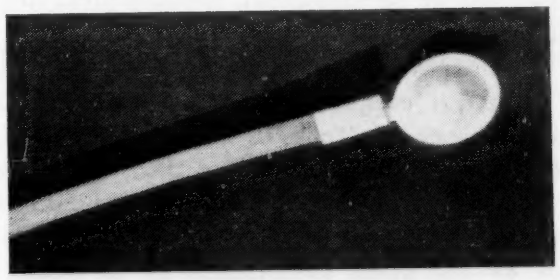

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ADEY, W. R., MERRILLEES, N. C. R. and SUNDERLAND, S. The entorhinal area; behavioural, evoked potential, and histological studies of its interrelationships with brain-stem regions. *Brain*, **1956**, *79*: 414-438.

ALAJMO, A., PASCAL, A. e SERRA, C. L'anoftalmo congenito nel quadro della "desplasia congenita encefalo-oftalmica" di Krause. Contributo clinico e studio elettroencefalografico. *G. Ital. Oftal.*, **1956**, *9*: 359-388.

ALLEN, I. M. The emotional factor and the epileptic attack. *N. Zealand med. J.*, **1956**, *105*: 297-308.

AMBROSIO, L., SERRA, C. e MAZZA, V. L'elettroencefalogramma nel saturnismo professionale (Contributo clinico alla patologia neurologica dell'intossicazione da piombo). *Acta Neurol.*, Napoli, **1956**, *11*: 3-25.

ANGELERI, F. e CARRERAS, M. Problemi de fisiologia dell'olfatto. Studio elettrofisiologico della vie contrifughe d'origine paleocorticale. *Riv. Neurobiol.*, **1956**, *2*: 255-273.

BALDWIN, M. Effects of hypothermia on epileptiform activity in the primate temporal lobe. *Science*, **1956**, *124*: 931-932.

BENTE, D. Elektroencephalographische Ergebnisse zur Wirkungsweise der neuroleptischen Behandlungsverfahren. *Encéphale*, **1956**, *45*: 898-903.

BONNET, H. Chlorpromazine et modifications de l'électro-encéphalogramme chez les malades mentaux. *Encéphale*, **1956**, *45*: 858-876.

BROGLIA, S. e POSTIR, A. Aspetti elettro-encéfalografici di 100 tumori della fossa posteriore e 40 del terzo ventricolo. *Riv. Neurol.*, **1956**. *26*: 29-50.

BUSCH, H. Cholinergic effects of β-substituted derivatives of pyruvic acid. *Science*, **1956**, *124*: 981-982.

CARRERAS, M. e ANGELERI, F. Problemi di fisiologia dell'olfatto. Una ipotesi sulla regolazione centrale dell'attività afferente nel sistema olfattivo. *Riv. Neurobiol.*, **1956**, *2*: 275-297.

CHARDON, G. Action du 3.697 RP (flaxédil) sur l'électroencéphalogramme du chien. *C. R. Soc. Biol.*, Paris, **1956**, *150*: 525-527.

CHATFIELD, P. O. *Fundamentals of Clinical Neurophysiology*. Springfield: Thomas, **1956**, 384 pp.

CHIARAMONTI, E. e SFERLAZZO, R. Ulteriore contributo alla conoscenza della sindrome cerebello-mioclono-epilettica, osservazioni cliniche, elettroencefalografiche ed elettromiografiche. *Riv. Patol. nerv. ment.* **1956**, *76*: 345-371.

COHEN, P. and HANNIGAN, H. M. "Aphasia" in cerebral palsy. *Amer. J. Phys. Med.*, **1956**, *35*: 218-222.

CORDAY, E., ROTHENBERG, S. and WEINER, S. M. Cerebral vascular insufficiency. *Arch. int. Med.*, **1956**, *98*: 683-690.

DEBRE, R., ROYER, P. and LESTRADET, H. Metabolic significance of nervous symptoms due to attacks of vomiting with ketosis in children. *J. Pediat.*, **1956**, *48*: 409-437.

DECARO, D., PICCIAU, R. e MULAS, L. Rilievi elettroencefalografici su di uncaso di sclerosi tuberosa. *Acta Neurol.*, Napoli, **1956**, *11*: 191-195.

DELAY, J., SCHULLER, E., DROSSOPOULO, G., HAIM, A., CHANOIT, P., VERDEAUX, G. et VERDEAUX, J. Un nouvel activant de l'électroencéphalogramme: le N.P. 13. *C. R. Soc. Biol.*, Paris, **1956**, *150*: 242-243.

DESPINOY, M. et SAUCET, D. Effets électro-encéphalographiques des stimulations auditives et lumineuses sur des sujets soumis à la chlorpromazine. *Encéphale*, **1956**, *45*: 877-883.

DEVORE, R. N., COLE, E. L. and TUMARKIN, B. Visceral pain associated with abnormal electroencephalographic findings in patients and siblings: report of one case of abdominal epilepsy. *J. Pediat.*, **1955**, *47*: 231-233.

DREYFUS-BRISAC, C. et BLANC, C. Electro-encéphalogramme et maturation cérébrale. *Encéphale*, **1956**, *45*: 205-245.

EFRON, R. The effect of olfactory stimuli in arresting uncinate fits. *Brain*, **1956**, *79*: 267-281.

EHRLICH, S. K. and KEOGH, R. P. The psychopath in a mental institution. *Arch. Neurol. Psychiat.*, Chicago, **1956**, *76*: 286-295.

Ey, H., Faure, H. et Lairy, G. C. Action du Largactil sur l'électro-encéphalogramme de malades mentaux chroniques comparée à l'action des barbituriques. *Encéphale*, **1956**, *45*: 843-852.

Farrari, E. Ricerche corticografiche sull'epilessia reflessa de eccitamenti afferenti di Amantea. *Acta Neurol.*, Napoli, **1956**, *11*: 58-65.

Feiring, E. H. and Sussman, B. J. Spontaneous occlusion of the middle cerebral artery. *Neurol.*, **1956**, *6*: 529-546.

Fisher, A. E. Maternal and sexual behavior induced by intracranial chemical stimulation. *Science*, **1956**, *124*: 228-229.

Gangloff, H. und Monnier, M. Bestimmung der elektrischen Erregbarkeit von Cortex, Diencephalon und Rhinencephalon beim Kaninchen. (Kombinierte Reiz - und Ableittechnik für pharmakologische Untersuchungen.) *Pflüg. Arch. ges. Physiol.*, **1955**, *261*: 421-433.

Gareiso, A. Valoración de la electroencefalografía en clínica neuropediátrica. *Arch. Pediat.*, Uruguay, **1955**, *26*: 119-127.

Glaser, G. H. and Dixon, M. S. Psychomotor seizures in childhood. A clinical study. *Neurol.*, **1956**, *6*: 646-655.

Glotfelty, J. S. and Wilson, W. P. Effects of tranquilizing drugs on reticular system activity in man. *North Carolina Med. J.*, **1956**, *17*: 401-405.

Grafstein, B. Mechanism of spreading cortical depression. *J. Neurophysiol.*, **1956**, *19*: 154-171.

Green, J. R. and Steelman, H. F. *Epileptic seizures.* Baltimore: Williams & Wilkins Co., **1956**, 165 p.

Higgins, J. W., Mahl, G. F., Delgado, J. M. R. and Hamlin, H. Behavioral changes during intracerebral electrical stimulation. *Arch. Neurol. Psychiat.*, Chicago, **1956**, *76*: 399-419.

Hill, D. Chap. 12, ''Electroencephalography'', in Brain, R. and Strauss, E. B. (Ed.) *Recent Advances in Neurology and Neuropsychiatry.* London: Churchill, **1955**, Sixth Edition, 178-231.

Hill, D. Clinical applications of EEG in psychiatry. *J. ment. Sci.*, **1956**, *102*: 264-271.

Hughes, J. R., Evarts, E. V. and Marshall, W. H. Post-tetanic potentiation in the visual system of cats. *Amer. J. Physiol.*, **1956**, *186*: 483-487.

Inghirami, L. e Muratorio, A. Sull'azione dell'alfacloralosio nell'individuo adulto normale. *Riv. Neurobiol.*, **1956**, *2*: 161-180.

Kalyanasundaram, V. Idiopathic epilepsy and its probable mode of origin from subcortical level. *Antiseptic*, **1956**, *53*: 675-686.

Kennard, M. A. Epileptic tendencies of the normal monkey. *Neurol.*, **1956**, *6*: 563-573.

Kruger, L. Characteristics of the somatic projection to the precentral cortex in the monkey. *Amer. J. Physiol.*, **1956**, *186*: 475-482.

Kuwana, S. Effects of reserpine and serpetin on the EEG of rabbits. *Acta med. biol.*, Niigata, **1956**, *4*: 21-29.

Lamarche, A., Roussel, A. et Rosendorf, Mme. Comparaisons des résultats obtenus par la cure de sommeil, la cure de somnolence, et la cure à la chlorpromazine seule et à dose élevée. Résultats de quelques électro-encéphalogrammes de contrôle. *Encéphale*, **1956**, *45*: 884-890.

Lennartz, H. Leistungsfähigkeit und Grenzen der klinischen Elektroencephalographie. *Elektro-Med.*, **1956**, *1*: 163-174.

Lennox, M. A. Geniculate and cortical responses to colored light flash in cat. *J. Neurophysiol.*, **1956**, *19*: 271-279.

Leroy, C. et Sigwald, J. Les myoclonies et épilepsies apparaissant chez certains malades au cours de l'administration de la chlorpromazine. *Encéphale*, **1956**, *45*: 904-909.

Li, C. L., Cullen, C. and Jasper, H. H. Laminar microelectrode studies of specific somatosensory cortical potentials. *J. Neurophysiol.*, **1956**, *19*: 111-130.

Li, C. L., Cullen, C. and Jasper, H. H. Laminar microelectrode analysis of cortical unspecific recruiting responses and spontaneous rhythms. *J. Neurophysiol.*, **1956**, *19*: 131-143.

Longman, J. e Tenuto, R. A. Mutismo acinético. *Arq. neuro-psiquiat.*, S. Paulo, **1956**, *14*: 213-225.

Lonnum, A. Guillain-Barre syndrome with prominent spinal and cerebral phenomena. *Acta psychiat.*, Kbh., **1956**, *31*: 261-271.

Low, N. L., Gibbs, E. L. and Gibbs, F. A. Electroencephalographic findings in breath holding spells. *Pediatrics*, **1955**, *15*: 595-599.

LUFT, U. C. and NOELL, W. K. The manifestations of sudden brief anoxia in man. *School of Aviation Medicine*, USAF, Report No. 55-86, January **1956**.

MCCULLAGH, W. H. and INGRAM, W. Headaches and hot tempers. *Dis. nerv. Syst.*, **1956**, *17*: 279-281.

MACHNE, X. and SEGUNDO, J. P. Unitary responses to afferent volleys in amygdaloid complex. *J. Neurophysiol.*, **1956**, *19*: 232-240.

MALIS, L. I. and KRUGER, L. Multiple response and excitability of cat's visual cortex. *J. Neurophysiol.*, **1956**, *19*: 172-186.

MANN, L. B. and WENDLAND, L. V. Correlation of continuous rapid infrared CO_2 analysis with the hyperventilation test in routine electroencephalography. *Bull. Los Angeles Neurol. Soc.*, **1956**, *21*: 84-89.

MATSON, D. B. Cerebellar astrocytoma in childhood. *Pediatrics*, **1956**, *18*: 150-158.

MAYER, S. E. and BAIN, J. A. The intracellular localization of fluorescent convulsants. *J. Pharm. exp. Ther.*, **1956**, *118*: 1-16.

MAYER, S. E. and BAIN, J. A. Localization of the hematoencephalic barrier with fluorescent quaternary acridones. *J. Pharm. exp. Ther.*, **1956**, *118*: 17-25.

MEULDERS, M. A propos de la paramyotonie au froid. Etude clinique et électroencéphalographique. *Acta neurol. psychiat. Belg.*, **1956**, *56*: 684-691.

MILONE, F. F. et GOMIRATO, G. Observations expérimentales sur le comportement de l'activité corticale spontanée sous l'action des neuroleptiques. *Encéphale*, **1956**, *45*: 853-857.

MONROE, R., JACOBSON, G. and ERVIN, F. Activation of psychosis by a combination of scopolamine and alpha-chloralose. *Arch. Neurol. Psychiat.*, Chicago, **1956**, *76*: 536-548.

MORRIS, A. A. Temporal lobectomy with removal of uncus, hippocampus, and amygdala. *Arch. Neurol. Psychiat.*, Chicago, **1956**, *76*: 479-496.

MURATORIO, A. e INGHIRAMI, L. L'Alfa cloralosio come attivante in EEG clinica. *Riv. Neurobiol.*, **1956**, *2*: 235-254.

NAKAO, H. and KOELLA, W. P. Influence of nociceptive stimuli on evoked subcortical and cortical potentials in cat. *J. Neurophysiol.*, **1956**, *19*: 187-195.

NAQUET, R. et PRUVOT, Ph. Essai d'interprétation de quelques variations des réponses EEG induites par la stimulation lumineuse intermittente chez l'homme. *C. R. Soc. Biol.*, Paris, **1956**, *150*: 1232-1233.

NIHEI, J. Electroencephalographic findings in rickets and in tetany. *Tohoku J. exp. Med.*, **1956**, *64*: (Suppl. IV), 311-328.

NOELL, W. K., CHINN, H. I. and HABERER, C. E. Electroencephalographic evaluation of the sedative effects of antihistaminic drugs. *School of Aviation Medicine*, USAF, Report No. 55-35, November **1955**.

OGDEN, T. E., AIRD, R. B. and GAROUTTE, B. C. The nature of bilateral and synchronous cerebral spiking. *Acta psychiat.*, Kbh., **1956**, *31*: 273-284.

O'LEARY, J. L. Speculative trends in electrophysiology. *Arch. Neurol. Psychiat.*, Chicago, **1956**, *76*: 187-197.

PAMPIGLIONE, G. and KERRIDGE, J. EEG abnormalities from the temporal lobe studied with sphenoidal electrodes. *J. Neurol. Neurosurg. Psychiat.*, **1956**, *19*: 117-129.

PASSOUANT, P., PASSOUANT-FONTAINE, TH. et CADILHAC, J. Les effets de la réserpine sur le comportement et les rythmes corticaux et rhinencéphaliques du chat chronique. *C. R. Soc. Biol.*, Paris, **1956**, *150*: 779-782.

PASSOUANT, P., PELISSIER, Mlle, MINVIELLE, J. et DUTARTRE. Modifications électro-encéphalographiques provoquées par la chlorpromazine au cours de l'épilepsie et de la schizophrénie. *Encéphale*, **1956**, *45*: 891-897.

PETERS, J. J., VONDERAHE, A. R. and PALMISANO, P. A. A use of the salamander for investigating and testing the anticonvulsant properties of drugs. *J. Pharm. exp. Ther.*, **1956**, *118*: 90-99.

PETERSEN, M. C., DODGE, H. W., JR., SEM-JACOBSEN, C. W., LAZARTE, J. A. and HOLMAN, C. B. Clinical results of selective leukotomy based on intracerebral electrography. *J. Amer. med. Ass.*, **1955**, *159*: 774-775.

Physiology of voluntary muscle. *Brit. med. J.*, (Sept.) **1956**, *12*: 161-236.

PIERCE, C. M. and LIPCON, H. H. Somnambulism: Electroencephalographic studies and related findings. *U. S. Armed Forces Med. J.*, **1956**, *7*: 1419-1426.

PIERCE, C. M., LIPCON, H. H., MCLARY, J. H. and NOBLE, H. F. Enuresis: Clinical, laboratory, and electroencephalographic studies. *U. S. Armed Forces Med. J.*, **1956**, *7*: 208-219.

PRESTON, J. B. Effects of chlorpromazine on the central nervous system of the cat: a possible neural basis for action. *J. Pharm. exp. Ther.*, **1956**, *118*: 100-115.

PURPURA, D. P. A neurohumoral mechanism of reticulo-cortical activation. *Amer. J. Physiol.*, **1956**, *186*: 250-254.

RAE, J. M. Report of the committee on training and standards for electroencephalographers. *Canad. Psychiat. Ass. J.*, **1956**, *1*: 191-193.

RAGNAR, G. and PHILLIPS, C. G. Excitatory and inhibitory processes acting upon individual Purkinje cells of the cerebellum in cats. *J. Physiol.*, **1956**, *133*: 520-547.

RAO, K. S. and PRICHARD, J. S. Photogenic epilepsy. *J. Pediat.*, **1955**, *47*: 619-623.

RUPPRECHT und SPUNDA, CH. Uber die Myoklonusepilepsie. *Wien. Zschr. Nervenh.*, **1956**, *12*: 359-372.

SANABRA, F. R. Aspectos electroencefalográficos del síndrome de Cushing. *Bol. Inst. Patol. Med.*, **1955**, *10*: 211-215.

SCHWADE, E. D. and GEIGER, S. G. Abnormal electroencephalographic findings in severe behavior disorders. *Dis. nerv. Syst.*, **1956**, *17*: 307-317.

SEM-JACOBSEN, C. W., PETERSEN, M. C., DODGE, H. W., JR., JACKS, Q. D., LAZARTE, J. A. and HOLMAN, C. B. Electric activity of the olfactory bulb in man. *Amer. J. med. Sci.*, **1956**, *232*: 243-251.

SENISE, T. Vecchie e nuove conoscenze su l'epilessia del lobo temporale. *Cervello*, **1956**, *32*: 65-99 e 147-211.

SERRA, C. Azione sull'elettroencefalogramma normale a patologico di un nuovo analettico iniettabile (dietilamide 3 etossi - 4 idrossibenzoica). *Acta Neurol.*, Napoli, **1955**, *10*: 956-965.

SERRA, C. e PIRO, S. Reperti semeiotici particolari in un caso di epilessia temporale profonda. *Acta Neurol.*, Napoli, **1955**, *10*: 966-982.

SERRA, C. e SCOPPA, A. Contributo alla conoscenza delle interrelazioni funzionali talamocorticali. *Acta Neurol.*, Napoli, **1955**, *10*: 10-19.

SIMON, C. W. and EMMONS, W. H. EEG, consciousness, and sleep. *Science*, **1956**, *124*: 1066-1069.

SISSON, B. D. and ELLINGSON, R. J. The EEG in cerebral atrophy. *J. nerv. ment. Dis.*, **1956**, *123*: 244-248.

STRAUSS, H. The electroencephalogram in the evaluation of head injuries without gross neurological deficit. *J. Hillside Hosp.*, **1956**, *5*: 268-281.

TERZIAN, H. Etude expérimentale de l'action de la Réserpine (Serpasil) sur les structures nerveuses centrales. *Encéphale*, **1956**, *45*: 835-842.

TERZUOLO, C. A. and GERNANDT, B. E. Spinal unit activity during synchronization of a convulsive type (strychnine tetanus). *Amer. J. Physiol.*, **1956**, *186*: 263-270.

THIGPEN, C. H. and MOSS, B. F. Unusual paranoid manifestations in a case of psychomotor epilepsy and narcolepsy. *J. nerv. ment. Dis.*, **1955**, *122*: 381-385.

TOWE, A. D. Evoked potentials and phenomena of the somatosensory cortex. *Confinia Neurol.*, **1956**, *16*: 333-354.

TURNER, M. La electroencefalografía en la arteroesclerosis cerebral. *Rev. Oto-Neur. Sud-Amer.*, **1955**, *30*: 105-108.

WALKER, A. E., POGGIO, G. F. and ANDY, O. J. Structural spread of cortically-induced epileptic discharges. *Neurol.*, **1956**, *6*: 616-626.

WALSH, R. R. Single cell spike activity in the olfactory bulb. *Amer. J. Physiol.*, **1956**, *186*: 255-257.

WELLS, C. E. Chronic hypoventilation in an epileptic patient. *Neurol.*, **1956**, *6*: 744-749.

WERNER, G. The central actions of chlorpromazine. *Encéphale*, **1956**, *45*: 920-926.

WHELAN, J. L., HADDAD, B. J., WEBSTER, J. E. and GURDJIAN, E. S. Electroencephalographic findings in subdural hematoma. *Grace Hosp. Bull.*, **1956**, *34*: 11-17.

WHITE, R. P. and SAMSON, F. E., JR. Effects of fatty acid anions on the electroencephalogram of unanesthetized rabbits. *Amer. J. Physiol.*, **1956**, *186*: 271-274.

WINFIELD, D. L., HUGHES, J. G. and SAYLE, W. E. Electroencephalography — Sleep findings in cerebral palsy. *Pediatrics*, **1955**, *16*: 88-92.

Supplement No. 5 of THE EEG JOURNAL is Now Available

SYSTÉMATIQUE ET ÉLECTROENCÉPHALOGRAPHIE DES ENCÉPHALITES ET ENCÉPHALOPATHIES

by

J. RADERMECKER

Neurologist and Electroencephalographer.
The Bunge Institute, Antwerp, Belgium.

243 pages, 78 plates and figures. Published by Masson and Co., Paris, 1956.

Forword by H. Fischgold and H. Gastaut. Preface by L. Van Bogaert. Chapter headings are as follows: Introduction. I — The concept of encephalitis and postinfectious encephalopathy. II — Classification and types of encephalitis. III — Acute meningitis and meningo-encephalitis of so called viral origin. IV — Subacute and chronic meningo-encephalitides. V — The primary encephalitides. VI — Postinfectious encephalitides. VII — Postinfectious and toxic encephalopathies. Conclusions. Bibliography.

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ANNOUNCEMENT

First International Congress of Neurological Sciences

Brussels, July 21st - 28th, 1957

Fourth International Congress of Electroencephalography and Clinical Neurophysiology.

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Berchem-Antwerp, Belgium.

PROVISIONAL AGENDA

Addition information. (EEG Journal Clin. Neurophysiol., Aug. 1956, Vol. VIII, No. 3, pp. 370 and 426).

Saturday, July 20th:

3 p.m. - 6 p.m.: Meeting of the Executive Committee of the International Federation of Societies for Electroencephalography and Clinical Neurophysiology, under the chairmanship of GREY WALTER (President of the International Federation).

6 p.m. - 7 p.m.: Meeting of the Editorial Board of the EEG Journal, under the direction of HERBERT H. JASPER, Editor-in-Chief of the Journal and Honorary-President of the International Federation.

Sunday, July 21st:

Morning: 10 a.m.: Meeting under the auspices of the International League Against Epilepsy.
Follow-up discussion of the Symposia held in Marseilles and Washington.

Topic: "SUB-CORTICAL AND TEMPORAL EPILEPSY".

A. EARL WALKER (U.S.A.): "Electroencephalographic and clinical manifestations of Epilepsy during the seizure: their significance in a dynamic conception of the Epilepsies in contrast to the present static classifications".

Afternoon: Opening Session of the First International Congress of Neurological Sciences.

Evening : RECEPTION.

Monday, July 22nd:

First Joint Meeting of the First International Congress of Neurological Sciences dedicated to the Memory of *Sir Charles Sherrington.*

Topic: "EXTRAPYRAMIDAL PATHOLOGY". Director: R. GARCIN (France).

R. GARCIN: "Evocation of Sir Charles Sherrington".

1. FRED A. METTLER (U.S.A.): "Anatomy and Physiology of the Extrapyramidal Motor Passage".
2. J. G. GREENFIELD (Great-Britain): "The Main Lesional Aspects of Extrapyramidal Diseases". Discussants: R. HASSLER (Germany). J. O. TRELLES (Peru).
3. R. GRANIT (Sweden): "Systems for control of Movement". Discussant: R. S. SCHWAB (U.S.A.).
4. PAUL C. BUCY and A. EARL WALKER (U.S.A.): "Physiological principles and results of Neurosurgical Interventions in Extrapyramidal Diseases". Discussants: H. NARABAYASHI (Japan). G. GUIOT (France).
5. DEOLINDO COUTO and PAULINO LONGO (Brazil): "Medical Treatment of Extrapyramidal Diseases". Discussants: J. N. CUMINGS (Great-Britain). J. SIGWALD (France).

Tuesday, July 23rd:

Second Joint Meeting of the First International Congress of Neurological Sciences dedicated to the Memory of *J. Babinski.*

Topic: "STATES OF CONSCIOUSNESS IN NEUROLOGY". Director: Sir GEOFFREY JEFFERSON (Great-Britain).

Sir GEOFFREY JEFFERSON: "Evocation of J. Babinski".

1. W. PENFIELD (Canada): "Alterations of Consciousness produced by Neurological Disorders".
2. TH. ALAJOUANINE (France): "Semeiology of States of Consciousness in Neurology". Discussant: J. AJURIAGUERRA (France).
3. F. BREMER (Belgium): "Some Problems raised by the Physiopathology of Consciousness". Discussants: MARY A. B. BRAZIER (U.S.A.). A. KREINDLER (Roumania).
4. H. ORTHNER (Germany): "Pathological Anatomy of Altered Consciousness of Hypothalamic Origin".
5. J. D. FRENCH (U.S.A.): "Some Contributions of the Physiological Laboratory to Problems in Consciousness".
6. SABINA STRICH (Great-Britain): "Altered States of Consciousness due to White Matter Degeneration".
7. SHEILA SHERLOCK (Great-Britain): "Altered Consciousness in Liver Failure".

ANNONCE

Premier Congrès International des Sciences Neurologiques

Bruxelles, 21-28 juillet 1957

IVe Congrès International d'Electroencéphalographie et de Neurophysiologie clinique.

Comité de Patronage:

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Ve Réunion de la Ligue Internationale contre l'Epilepsie.

Comité de Patronage:

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Berchem-Anvers, Belgique.

PROGRAMME PROVISOIRE

Complément aux renseignements préliminaires. (Voir EEG Journal Clin. Neurophysiol., août 1956, Vol. VIII, no 3, pp. 370 et 426).

Samedi, 20 juillet:

15-18 h.: Réunion du Comité Exécutif de la Fédération Internationale d'Electroencéphalographie et de Neurophysiologie clinique, sous la Présidence de GREY WALTER (Président de la Fédération Internationale).

18-19 h.: Réunion du Bureau d'édition du Journal d'Electroencéphalographie et de Neurophysiologie clinique, sous la direction de H. JASPER, Editeur en chef du Journal et Président d'honneur de la Fédération Internationale.

Dimanche, 21 juillet:

Matin: à 10 h.: Réunion sous les auspices de la Ligue Internationale contre l'Epilepsie.
Conclusions des Symposia de Marseille et de Washington.

Thème: "L'EPILEPSIE SOUS-CORTICALE ET L'EPILEPSIE TEMPORALE".

A. EARL WALKER (Etats-Unis): "Manifestations électroencéphalographiques et cliniques des épilepsies pendant les crises. Leur utilisation pour une conception dynamique des épilepsies en opposition avec les classifications statiques actuelles".

Après-midi: Ouverture solennelle du 1er Congrès International des Sciences Neurologiques.

Soir: RECEPTION D'ACCUEIL

Lundi, 22 juillet:

Première Journée commune du 1er Congrès International des Sciences Neurologiques dédiée à la mémoire de *Sir Charles Sherrington*.

Thème: "LA PATHOLOGIE EXTRAPYRAMIDALE". Directeur: R. GARCIN (France).

R. GARCIN: "Evocation de Sir Charles Sherrington".

1. FRED A. METTLER (Etats-Unis): "Anatomie et physiologie des voies motrices extrapyramidales".
2. J. G. GREENFIELD (Grande-Bretagne): "Les principaux aspects lésionnels des affections du système extrapyramidal". Discussion: R. HASSLER (Allemagne), J. O. TRELLES (Pérou).
3. R. GRANIT (Suède): "Les systèmes pour le contrôle du mouvement".
Discussion: R. S. SCHWAB (Etats-Unis).
4. P. C. BUCY et A. EARL WALKER (Etats-Unis): "Principes physiologiques et résultats des interventions neurochirurgicales dans les affections dites extrapyramidales". Discussion: H. NARABAYASHI (Japon), G. GUIOT (France).
5. D. COUTO et P. LONGO (Brésil): "Le traitement médical des maladies dites extrapyramidales".
Discussion: J. N. CUMINGS (Grande-Bretagne).
J. SIGWALD (France).

Mardi, 23 juillet:

Deuxième Journée commune du 1er Congrès International des Sciences Neurologiques dédiée à la mémoire de *J. Babinski*.

Thème: "LES ETATS DE CONSCIENCE EN NEUROLOGIE". Directeur: Sir GEOFFREY JEFFERSON (Grande-Bretagne).

Sir GEOFFREY JEFFERSON: "Evocation de J. Babinski".

1. W. PENFIELD (Canada): "Les altérations de la conscience dues aux désordres neurologiques".
2. Th. ALAJOUANINE (France): "Sémiologie des états de conscience en neurologie".
Discussion: J. AJURIAGUERRA (France).
3. F. BREMER (Belgique): "De quelques problèmes posés par la physiopathologie des altérations de la conscience". Discussion: M. A. B. BRAZIER (Etats-Unis), A. KREINDLER (Roumanie).
4. H. ORTHNER (Allemagne): "Anatomie pathologique des troubles de la conscience d'origine hypothalamique".
5. J. D. FRENCH (Etats-Unis): "Contributions physiologiques expérimentales aux problèmes de la conscience".
6. SABINA STRICH (Grande-Bretagne): "Altérations des états de conscience dues à la dégénérescence de la matière blanche".
7. SHEILA SHERLOCK (Grande-Bretagne): "Altérations de la conscience dans les états hépathiques graves".

8. PERCIVAL BAILEY (U.S.A.): ''Neurosurgical Data on States of Consciousness''.
   Discussant: Sir FRANCIS WALSHE (Gr.-Britain).
9. R. JUNG (Germany): ''Neurophysiology and Normal Changes in Consciousness''.
10. H. FISCHGOLD (France): ''Pathology of Changes in Consciousness''.
    Discussant: ARNE LUNDERVOLD (Norway).
11. V. M. BUSCAIN (Italy): ''Present Neurological Theories of States of Consciousness''.
    Discussant: Sir RUSSELL BRAIN (Great-Britain).

Wednesday, July 24th:

Morning: 9 a.m. - 1 p.m.: Meeting of the Fourth International Congress of Electroencephalography and Clinical Neurophysiology.

Symposium on Electromyography.

Topic: ''THE INTERPRETATION OF NORMAL AND PATHOLOGICAL MUSCLE POTENTIALS''. Director: A. FESSARD (France).

1. F. BUCHTAL (Denmark): ''The Functional Organization of the Motor Unit''.
2. ISCH (France): ''Contribution of Electromyography in Motor Disturbances''.
   Discussant: BAUMGARTNER (France).
3. J. SCHERRER, J. LEFEBVRE and A. BOURGUIGNON (France): ''Electromyographic Aspects of Muscular Fatigue''.
   Discussant: A. PAILLARD (France).

Afternoon: 3 p.m. - 7 p.m.: Meeting of the Fourth International Congress of Electroencephalography and Clinical Neurophysiology.

Symposium: ''ONTOGENESIS OF THE ELECTROENCEPHALOGRAM IN HUMAN AND ANIMAL''. Director: J. KNOTT (U.S.A.).

1. P. KELLAWAY (U.S.A.): ''The Development of the EEG in Man and Animals''.
   Discussants: CH. HENRY (U.S.A.), D. A. POND (Great-Britain), CHASKIEL-GROSSMAN (U.S.A), DREYFUS-BRISAC (France), SCHAPER (Germany).

Thursday, July 25th:

Morning: 9 a.m. - 1 p.m.: Session of the Fourth International Congress of Electroencephalography and Clinical Neurophysiology.

Symposium: ''ELECTROENCEPHALOGRAPHIC ''ABNORMALITIES'' AS SIGNS OF LOCALIZED BRAIN PATHOLOGY''. Director: GREY WALTER (Great-Britain).

1. H. TERZIAN (Italy): ''EEG Abnormalities at the Site of the Lesion''.
2. W. A. COBB (Great-Britain): ''EEG Abnormalities at a Distance from the Lesion''.
3. R. NAQUET (France) and J. GREEN (U.S.A.): ''The Study of Epileptic discharges in connection with Cerebral Localized Lesions (Local and remote discharges)''.
4. H. W. STEINMANN (Germany): ''Abnormalities in close contact with and in the vicinity of the Lesion (Corticography and subcorticography)''.
   Discussant: R. JANZEN (Germany).

Afternoon: 3 p.m. - 7 p.m.: Joint Meeting of the Fourth International Congress of Electroencephalography and Clinical Neurophysiology with the International League Against Epilepsy.

Topic: ''PATHOGENESIS AND CLINICAL ASPECTS OF PETIT MAL EPILEPSY''. Director: F. A. GIBBS (U.S.A.).

1. J. DROOGLEEVER-FORTUYN (Holland): ''Physiopathogeny of Petit Mal''.
2. A. KREINDLER (Roumania): ''Present Electroencephalographic Considerations about Petit Mal''.
   Discussants: Sir CHARLES SYMONDS (Great-Britain), R. G. BICKFORD (U.S.A.), D. INGVAR (Sweden), R. JUNG (Germany), A. SUBIRANA and L. OLLER DAURELLA (Spain).

Friday, July 26th:

Morning: 9 a.m. - 1 p.m.: Session of the Fourth International Congress of Electroencephalograply and Clinical Neurophysiology.

Symposium: ''ELECTROENCEPHALOGRAPHIC STUDY OF CONDITIONING''. Director: H. GASTAUT (France).

1. H. YOSHII and J. MATSUMOTO (Japan): ''Electroencephalographic Study of Conditioning in Animals''. Discussants: COURJON (France), JOUVET (France).
2. V. S. ROUSSINOV and G. D. SMIRNOV (U.S.S.R.): ''Electroencephalographic Study of Conditioning in Human''.
   Discussant: MUNDY CASTLE (South Africa).
3. R. H. W. COOPER, J. and H. W. SHIPTON, V. J. and GREY WALTER (Great-Britain): ''Analytical Methods of Studying conditioned Behaviour in Human Subjects''.
   Discussant: J. KNOTT (U.S.A.).
4. A. and C. JUS (Poland): ''Application of Electrocortical Conditioning to Mental Diseases: Diagnostic and Physiopathological Survey''.
   Discussant: A. KREINDLER (Roumania).

Afternoon: 3 p.m. to 7 p.m.: Meeting of the Fourth International Congress of Electroencephalography and Clinical Neurophysiology.

Symposium: ''ELECTROENCEPHALOGRAPHIC STUDY OF CONDITIONING'' (contd.). Director: H. GASTAUT (France).

1. F. MORRELL (U.S.A.): ''An Anatomical and Physiological Analysis of Electrocortical Conditioning''.
   Discussant: J. HRBEK (Czechoslovakia).
2. H. JASPER, B. DOANE and F. RICCI (Canada): ''Microphysiological Studies of Conditioning: Technique and Preliminary Results''.
   Discussant: A. FESSARD (France).
3. P. BUSER and A. ROGER (France): ''Interpretation of Conditioning based on Electroencephalographic Data''. Discussant: LISSAK (Hungary).

Saturday, July 27th:

Morning: 9 a.m. - 1 p.m.: Meeting of the Fourth International Congress of Electroencephalography and Clinical Neurophysiology. Presentation of Communications incorporated in Digests.

Afternoon: 2 p.m. to 5 p.m.: General Assembly of the Federation.

1. Report of the Secretary-General (H. GASTAUT).
2. Report of the Treasurer (M. A. B. BRAZIER).
3. Report on Special Activities (The President and others.)
4. Election of Officers.
5. Discussion on the date and site of the next International Congress.
6. Delegates to the General Assembly of the First International Congress of Neurological Sciences.

At 5.30 p.m.: General Assembly of the First International Congress of Neurological Sciences (1st I.C.N.S.).

Sunday, July 28th:

Celebration at Louvain of the Centenary of Arthur van Gehuchten's birth. (A detailed programm will be published later on).

N.B. — Further information has already been published in the preliminary announcements. There will be regular Bulletins issued as required.

8. PERCIVAL BAILEY (Etats-Unis): ''Les données chirurgicales sur les états de conscience''. Discussion: Sir FRANCIS WALSHE (Grande-Bretagne).
9. R. JUNG (Allemagne): ''Neurophysiologie et modifications normales de la conscience''.
10. H. FISCHGOLD (France): ''Pathologie des modifications de la conscience''.
    Discussion: ARNE LUNDERVOLD (Norvège).
11. V. M. BUSCAINO (Italie): ''Théories actuelles de la neurologie des états de conscience''. Discussion: Sir RUSSELL BRAIN (Grande-Bretagne).

Mercredi, 24 juillet:

Matin: 9-13 h.: Réunion du IVe Congrès International d'Electroencéphalographie et de Neurophysiologie clinique.

Symposium sur l'électromyographie.

Thème: ''L'INTERPRETATION DES POTENTIELS NORMAUX ET PATHOLOGIQUES EN ELECTROMYOGRAPHIE''. Directeur: A. FESSARD (France).

1. F. BUCHTAL (Danemark): ''L'organisation fonctionnelle de l'unité motrice''.
2. ISCH (France): ''L'apport de l'électromyographie dans les troubles moteurs''.
   Discussion: BAUMGARTNER (France).
3. J. SCHERRER, J. LEFEBVRE and A. BOURGUIGNON (France): ''Aspect électromyographique de la fatigue musculaire''.
   Discussion: A. PAILLARD (France).

Après-midi: 15 - 19 h.: Réunion du IVe Congrès International d'Electroencéphalographie et de Neurophysiologie clinique.

Simposium: ''L'ONTOGENESE DE L'ELECTROENCEPHALOGRAPHIE CHEZ L'HOMME ET L'ANIMAL''. Directeur: J. KNOTT (Etats-Unis).

1. P. KELLAWAY (Etats-Unis): ''Evolution ontogénique de l'EEG chez l'homme et l'animal''.
   Discussion: CH. HENRY (Etats-Unis), D. A. POND (Grande-Bretagne), CHASKIEL-GROSSMAN (Etats-Unis), DREYFUS-BRISAC (France), SCHAPER (Allemagne).

Jeudi, 25 juillet:

Matin: 9 - 13 h.: Réunion du IVe Congrès International d'Electroencéphalographie et de Neurophysiologie clinique.

Symposium: ''L'EEG EN RELATION AVEC LA PATHOLOGIE CEREBRALE LOCALISEE''. Directeur: GREY WALTER (Grande-Bretagne).

1. H. TERZIAN (Italie): ''Les anomalies au siège de la lésion''.
2. W. A. COBB (Grande-Bretagne): ''Les anomalies EEG à distance de la lésion''.
3. R. NAQUET (France) et J. GREEN (Etats-Unis): ''Etude des décharges épileptiques en relation avec les lésions cérébrales localisées (décharges locales et à distance)''.
   H. W. STEINMANN (Allemagne): ''Les anomalies directement enregistrées au contact et au voisinage de la lésion (cortico et sous-corticographie).
   Discussion: R. JANZEN (Allemagne).

Après-midi: 15 - 19 h.: Réunion commune du IVe Congrès International d'Electroencéphalographie et de Neurophysiologie clinique et de la Ligue Internationale contre l'Epilepsie.

Thème: ''LA PATHOLOGIE ET LES ASPECTS CLINIQUES DU PETIT MAL''. Directeur: F. A. GIBBS (Etats-Unis).

1. J. DROOGLEEVER-FORTUYN (Pays-Bas): ''Physiopathogénie du Petit Mal''
2. A. KREINDLER (Roumanie): ''Considérations élecencephalographic Considerations about Petit Mal et les états du Petit Mal''.
   Discussion: Sir CHARLES SYMONDS (Grande-Bretagne), R. G. BICKFORD (Etats-Unis), D. INGVAR (Suède), R. JUNG (Allemagne), A. SUBIRANA et L. OLLER-DAURELLA (Espagne).

Vendredi, 26 juillet:

Matin: 9 - 13 h.: Réunion du IVe Congrès International d'Electroencéphalographie et de Neurophysiologie clinique.

Symposium: ''L'ELECTROENCEPHALOGRAPHIE DU CONDITIONNEMENT''. Directeur: H. GASTAUT (France).

1. N. YOSHII et J. MATSUMOTO (Japon): ''Etude électroencéphalographique du conditionnement chez l'animal''. Discussion: COURJON (France), JOUVET (France).
2. V. S. ROUSSINOV et G. D. SMIRNOV (U.R.S.S.): ''Etude électroencéphalographique du conditionnement chez l'homme''.
   Discussion: MUNDY CASTLE (Afrique du Sud).
3. R. COOPER, H. W. et J. SHIPTON, V. J. et GREY WALTER (Grande-Bretagne). ''Méthodes analytiques de l'étude du comportement conditionné chez l'homme''.
   Discussion: J. KNOTT (Etats-Unis).
4. A. et C. JUS (Pologne): ''Application du conditionnement électrocortical à l'étude des maladies mentales: considérations diagnostiques et physiopathologiques''.
   Discussion: A. KREINDLER (Roumanie).

Après-midi: 15 - 19 h.: Réunion du IVe Congrès International d'Electroencéphalographie et de Neurophysiologie clinique.

Symposium: ''L'ELECTROENCEPHALOGRAPHIE DU CONDITIONNEMENT'' (suite). Directeur: H. GASTAUT (France).

1. F. MORRELL (Etats-Unis): ''Une analyse anatomique et physiologique du conditionnement électrocortical''.
   Discussion: J. HRBEK (Tchécoslovaquie).
2. H. JASPER, B. DOANE et F. RICCI (Canada): ''Etude microphysiologique du conditionnement: technique et résultats préliminaires''.
   Discussion: A. FESSARD (France).
3. P. BUSER et A. ROGER (France): ''Interprétation du conditionnement sur la base des données électroencéphalographiques''.
   Discussion: LISSAK (Hongrie).

Samedi, 27 juillet:

Matins 9 - 13 h.: Réunion du IVe Congrès International d'Electroencéphalographie et de Neurophysiologie clinique. Présentation des Communications sous forme de Digests.

Après-midi: 14 - 17 h.: Assemblée Générale de la Fédération.

1. Rapport du Secrétaire général (H. GASTAUT).
2. Rapport du Trésorier (M. A. B. BRAZIER).
3. Rapport des activités extraordinaires (le Président et autres).
4. Election du nouveau Bureau.
5. Décision concernant le siège et la date du prochain Congrès International.
6. Délégués à l'assemblée générale du 1er Congrès International des Sciences Neurologiques.

A 17 h. 30: Assemblée générale du 1er Congrès International des Sciences Neurologiques (1er C.I.S.N.).

Dimanche, 28 juillet:

Célébration à Louvain du Centenaire de la naissance de Arthur Van Gehuchten. (Le programme détaillé sera publié ultérieurement).

N.B. — Les autres renseignements ont déjà été communiqués dans les annonces préliminaires. Des bulletins seront régulièrement publiés, comme demandé.

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1. *Bibliography of Electroencephalography,* 1875-1948,

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   Montreal, 1950, 178 pages, price $3.25.

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   edited by H. FISCHGOLD, Paris, 1949, 137 pages, price $2.00.

3. *Third International Congress — Communications,*

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   C. HENRY, Cambridge, 1953, 94 pages, price $2.00.

4. *Third International Congress — Symposia,*

   edited by E. WALKER, J. MERLIS and C. HENRY,
   Cambridge, 1953, 260 pages, price $5.00.

5. *Encéphalites et Encéphalopathies,*

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   Masson & Cie, Paris, 1956, 243 pages, price $8.00.

6. *Conditionnement et Réactivité en Electroencéphalographie*

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   edited by H. FISCHGOLD and H. GASTAUT,
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